H. Smith Broadbent
Organic Chemistry Sub-Dept.
Brigham Young University

# ORGANIC SYNTHESES

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# ORGANIC SYNTHESES

AN ANNUAL PUBLICATION OF SATISFACTORY
METHODS FOR THE PREPARATION
OF ORGANIC CHEMICALS



*CONTRIBUTORS*

Other than members of the Board

Lawrence H. Amundsen
B. Abramovitch
Robert H. Baker
Alan Bell
Frederick G. Bordwell
Allen Buck
J. H. Clark
George H. Coleman
William B. Cook
William R. Darby
Duncan G. Foster
Oliver Grummitt
Walter H. Hartung
Jonathan L. Hartwell
C. R. Hauser
Kenneth L. Howard
B. E. Hudson
E. W. Kaiser
C. E. Kaslow
C. J. Kibler
J. Wayne Kneisley
W. M. Lauer
Nathan Levin
C. S. Maxwell
Chester M. McCloskey
A. V. McIntosh
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A. B. Nelson
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E. J. Rahrs
Byron Riegel
Edward Rietz
Anthony R. Ronzio
James J. Sanderson
Margaret K. Seikel
J. C. Shivers
Robert E. Steiger
John R. Totter
S. M. Tsang
J. Van Allan
T. D. Waugh
C. A. Weisgerber
Richard Weiss
A. Weissberger
Ennis B. Womack
Ernest H. Wood
Eugene H. Woodruff

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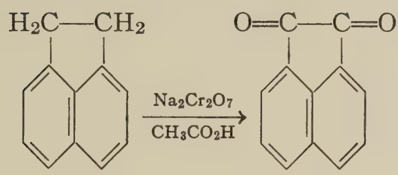
# TABLE OF CONTENTS

## ACENAPHTHENEQUINONE



Submitted by C. S. MAXWELL and C. F. H. ALLEN.
Checked by R. L. SHRINER and C. H. TILFORD.

### 1. Procedure

In a 2-l. three-necked round-bottomed flask, fitted with a mechanical stirrer, a reflux condenser, and a large-bore, short-stemmed funnel, are placed 30 g. (0.195 mole) of acenaphthene (Notes 1 and 2) and 210 ml. of glacial acetic acid. Stirring is started, and the mixture is heated to about 95°. The flame is then removed, and 130 g. (0.43 mole) of coarsely pulverized technical sodium dichromate is added through the funnel over a period of 15 to 30 minutes. The addition is made as fast as possible without causing such vigorous boiling that the reaction gets out of hand. If frothing starts, the flask is immediately surrounded by a pan of cold water. After all the dichromate has been added, the funnel is replaced by a stopper and the mixture refluxed for 15 minutes, during which time it becomes very viscous. Seven hundred milliliters of hot water is then added; the mixture is stirred for 10 minutes and filtered by suction. The red precipitate is washed on the filter with 400 ml. of hot water to remove chromium salts.

The solid is transferred to a 1-l. beaker, and 220 ml. of a 10% solution of sodium carbonate is added. The solution is heated on a steam bath for an hour and filtered hot; this operation removes the naphthalic anhydride formed as a by-product (Note 3). The residual red solid is then placed in a 2-l. three-

necked flask fitted with a stirrer and a reflux condenser, the top of which is attached to a gas trap for absorbing sulfur dioxide. Three hundred milliliters of a 40% sodium bisulfite solution is then added, and the mixture is refluxed with stirring for 45 minutes, whereupon 500 ml. of water is added and refluxing is continued for 10 minutes. The hot solution is filtered by suction. The filtrate is then heated to boiling and acidified by the slow, cautious addition of 110 ml. of concentrated sulfuric acid (Note 4). The mixture is digested for 15 minutes over a low flame and then filtered. The yellow precipitate is washed thoroughly with 200 ml. of water and 100 ml. of dilute ammonia (1 part concentrated ammonia to 10 parts of water by volume). The washed and dried acenaphthenequinone weighs 15–21 g. (42–60%) and melts at 243–245°.

## 2. Notes

1. The acenaphthene should be the finest grade obtainable since the technical brown variety gives tarry material from which it is difficult to isolate the quinone. The white acenaphthene obtained from the Gesellschaft für Teerverwertung, Duisburg-Meiderich, Germany, may be used. Acenaphthene produced by the Reilly Tar and Chemicals Company, Indianapolis, Indiana, is also satisfactory provided that it is recrystallized from methanol before use; the purified material melts at 94–95°.

2. Larger quantities (50–100 g.) of acenaphthene can be oxidized conveniently, but it is very difficult to extract all the quinone from the crude material. If larger quantities are oxidized, the product should be divided into small lots as described above for the bisulfite extraction. The yield is determined to a large extent by the thoroughness of the extraction.

3. The naphthalic anhydride (4–11 g.) is recovered on acidification of the filtrate. This substance is the principal product if the oxidation becomes too vigorous. Naphthalic anhydride may be prepared from the technical grade of acenaphthene.

4. The acidification should be done in a hood; much sulfur dioxide is evolved. Hydrochloric acid does not precipitate all the quinone.

### 3. Methods of Preparation

Acenaphthenequinone has been prepared from acenaphthene by oxidation with chromic acid,[1,2,3] with calcium permanganate,[4] with air in the presence of catalysts in various solvents,[5,6,7] and by the formation of an oxime with amyl nitrite followed by hydrolysis.[8]

## AMINOACETAL

### (Acetaldehyde, amino-, diethyl acetal)

$$BrCH_2CH(OC_2H_5)_2 + 2NH_3 \rightarrow H_2NCH_2CH(OC_2H_5)_2 + NH_4Br$$

Submitted by C. F. H. Allen and J. H. Clark.
Checked by H. R. Snyder, R. L. Rowland, and H. J. Sampson, Jr.

### 1. Procedure

To a solution of 197 g. (1 mole) of bromoacetal[1] in 250 ml. of absolute alcohol, cooled in a hydrogenation bomb of about 1.1-l. capacity to the temperature of a Dry Ice-acetone bath, is added approximately 300 g. (about 18 moles) of liquid ammonia (Note 1). The bomb is closed, connected with a pressure gauge, and heated at 120–130° with shaking for 12 hours. The pressure rises to about 2300 pounds.

After the bomb has cooled, the ammonia is allowed to escape (Note 2) and the solution is poured out. The bomb is rinsed with

[1] Gräbe, *Ber.*, **20**, 659 (1887); **25**, 654 (1892); *Ann.*, **276**, 3 (1893).
[2] Dashevskii and Karishin, *Org. Chem. Ind.* (*U.S.S.R.*), **1**, 729 (1936) [*C.A.*, **31**, 679 (1937)].
[3] Kiprianov and Dashevskii, *J. Applied Chem.* (*U.S.S.R.*), **7**, 944 (1934) [*C.A.*, **29**, 2530 (1935)].
[4] Morgan, *J. Soc. Chem. Ind.*, **49**, 420 (1930).
[5] Jaeger, Brit. pat. 318,617 [*C.A.*, **24**, 2145 (1930)].
[6] Duckert, *Arch. sci. phys. nat.*, **15**, 244 (1933) [*C.A.*, **28**, 1255 (1934)].
[7] Paillard, *Helv. Chim. Acta*, **16**, 775 (1933).
[8] Reissert, *Ber.*, **44**, 1750 (1911).

AMINOACETAL

[1] *Org. Syntheses*, **23**, 8 (1943); Bedoukian, *J. Am. Chem. Soc.*, **66**, 651 (1944).

two 200-ml. portions of absolute alcohol (Note 3), and the combined solution and washings are filtered. The alcohol is distilled from the filtrate at atmospheric pressure on the steam bath (Notes 4 and 5). The liquid residue is dissolved in 1.5 l. of ether, the inorganic solid which separates is filtered, and the ether is dried over 125 g. of potassium hydroxide pellets. The ether is evaporated and the residue is distilled at reduced pressure (Note 6). The material which distils below 180°/15 mm. is fractionated at atmospheric pressure in a modified Claisen flask. The material distilling below 161°, amounting to 15 g., is discarded. The aminoacetal distilling at 161–162° amounts to 43–52 g. (32–39%). The residue amounts to about 18 g. (Notes 7, 8, and 9).

## 2. Notes

1. The bomb is cooled by placing it in an iron pot of about two-thirds the height of the bomb. The pot is half filled with acetone, and pieces of Dry Ice are added until the vigorous evolution of carbon dioxide accompanying the addition of each new piece is no longer observed. If liquid ammonia is added to an insufficiently cooled solution of bromoacetal and alcohol, the ammonia is volatilized so vigorously that much of the starting material is lost. The checkers forced the ammonia from a small bomb into the bomb containing the alcohol and bromoacetal, at room temperature, by the aid of compressed hydrogen.[2]

2. Some of the reaction mixture may be carried from the bomb by the escaping ammonia. If the ammonia is allowed to escape through a tube leading into a beaker or flask, this material can be collected.

3. An appreciable amount of a slimy solid collects on the walls of the bomb. It appears to consist of ammonium bromide together with a small amount of iron salts dissolved from the walls of the bomb by the action of the ammonia. The amount of product recovered by careful working of this material is less than 2 g.

[2] *Org. Syntheses*, **23**, 69 (1943).

4. If much of the alcohol is left in the residue, the ether solution will deposit considerable amounts of inorganic salt during the drying over potassium hydroxide, and it will be desirable to filter rather than decant the ether solution. The yield is not affected.

5. A more elaborate procedure for working up this residue is as follows.

The residue is added to an equal volume (about 175 ml.) of water; the oil which separates is removed; and the water layer is extracted with two 150-ml. portions of ether. The water layer (A) is treated as described below. The extracts are dried over potassium hydroxide pellets, the ether distilled, and the residue fractionated. That portion (40 g.) of the distillate which comes over below 150°/15 mm. is refractionated at atmospheric pressure. The material (B) distilling below 180°, amounting to 19 g., is combined with the main portion of the product as indicated below.

The water layer (A) remaining from the ether extraction described above is treated with 175 g. of anhydrous potassium carbonate. The oil which separates is removed, and the water layer is extracted twice with 150-ml. portions of ether. The combined oil and extracts are dried over potassium hydroxide pellets and distilled at 15 mm. pressure. The material boiling below 180° at this pressure amounts to 63 g. This material is combined with the distillate (B) obtained above, and the whole is fractionated at atmospheric pressure. The material of b.p. 161–162° amounts to 50 g. (37%).

6. This material contains a considerable amount of dissolved solids from which it is desirable to remove the product at as low a temperature as possible.

7. The low-boiling fraction was not investigated. The residue is largely diacetalylamine (b.p. 124–127°/7 mm.) (11–14%).

8. Aminoacetal has been prepared from chloroacetal by this same procedure in a yield of 46%.

9. A procedure similar to the present one, in which potassium iodide is added to the reaction mixture, is reported to give slightly better yields.[3] The checkers found that addition of potassium

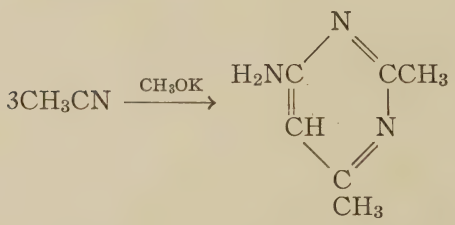
[3] Cass, *J. Am. Chem. Soc.*, **64**, 785 (1942).

iodide to the reaction mixture in the present procedure had no beneficial effect.

### 3. Methods of Preparation

Aminoacetal has been prepared by the action of ammonia on haloacetals,[3,4,5,6,7,8,9] by the reduction of nitroacetal using sodium in boiling alcohol,[10] and by the reduction of glycine ester hydrochloride with sodium amalgam.[11]

## 4-AMINO-2,6-DIMETHYLPYRIMIDINE



Submitted by ANTHONY R. RONZIO and WILLIAM B. COOK.
Checked by C. G. STUCKWISCH and HENRY GILMAN.

### 1. Procedure

Seventy grams (1 mole) of freshly prepared potassium methoxide (Note 1) and 41 g. (1 mole) of freshly purified acetonitrile (Note 2) are placed in a 500-ml. distilling flask. A cold-finger condenser which extends into the bulb of the flask is inserted through a rubber stopper in the neck of the flask, and a short

[4] Wohl, *Ber.*, **21**, 617 (1888); **39**, 1953 (1906).
[5] Wolff, *Ber.*, **21**, 1482 (1888); **26**, 1832 (1893).
[6] Wolff and Marburg, *Ann.*, **363**, 179 (1908).
[7] Marckwald, *Ber.*, **25**, 2355 (1892).
[8] Hartung and Adkins, *J. Am. Chem. Soc.*, **49**, 2521 (1927).
[9] Buck and Wrenn, *J. Am. Chem. Soc.*, **51**, 3613 (1929).
[10] Losanitsch, *Ber.*, **42**, 4049 (1909).
[11] Fischer, *Ber.*, **41**, 1021 (1908).

piece of rubber tubing carrying a Hofmann clamp is connected to the side arm of the flask. The tubing is connected to an aspirator, and suction is applied until the acetonitrile begins to boil, whereupon the tubing is closed by means of the clamp and the flask is heated for 5 hours in an oil bath maintained at 140°.

At the end of the heating period the contents of the flask will have solidified. To the cold mixture 40 ml. of water is added to hydrolyze the potassium methoxide and precipitate the pyrimidine; the fine crystals are filtered and dried. The crude product is placed in a 500-ml. distilling flask with 250 ml. of purified kerosene (Note 3). On distilling the kerosene, the pyrimidine codistils and solidifies in the receiving flask to a snow-white mass of crystals. These are filtered, washed well with petroleum ether, and dried in an oven at 100°. The yield of pure material, melting at 182–183°, is 27.5–28.7 g. (67–70%) (Note 4).

## 2. Notes

1. To prepare the potassium methoxide 39 g. (1 gram atom) of metallic potassium, cut *under toluene* (see p. 100) in 1-cm. cubes, is placed in a 1-l. three-necked flask which has been swept with nitrogen. The flask, fitted with a reflux condenser, mechanical stirrer, and dropping funnel, is immersed in a cooling bath at −30°, and absolute methanol is added through the funnel until all the potassium has dissolved. The excess methanol is removed by heating on the steam bath, finally under reduced pressure, and the potassium methoxide is dried overnight in a vacuum desiccator over sulfuric acid.

2. Commercial acetonitrile is treated with solid sodium carbonate until no more carbon dioxide is evolved. The nitrile is then distilled over phosphorus pentoxide and stored in tightly stoppered bottles. Before use, the nitrile is redistilled over phosphorus pentoxide.

3. Kerosene is purified by shaking for 24 hours with concentrated sulfuric acid. The kerosene is separated from the acid, washed several times with dilute sodium hydroxide, then with water, and finally dried over calcium chloride and distilled using

an air condenser. Purified kerosene is a water-white, sweet-smelling liquid.

4. The percentage yield decreases when larger or smaller quantities of material are used.

### 3. Methods of Preparation

4-Amino-2,6-dimethylpyrimidine has been prepared by heating the reaction product obtained from acetic anhydride and acetamidine;[1] by treating 4-chloro-2,6-dimethylpyrimidine with ammonia;[2] and by heating acetonitrile either with sodium ethoxide in a sealed tube[3] or with sodium.[4, 5]

[1] Pinner, *Ber.*, **22**, 1600 (1889).
[2] Schmidt, *Ber.*, **35**, 1577 (1902).
[3] Schwarze, *J. prakt. Chem.*, (2) **42**, 3 (1890).
[4] Keller, *J. prakt. Chem.*, (2) **31**, 365 (1885).
[5] von Meyer, *J. prakt. Chem.*, (2) **27**, 153 (1883).

## *dl*-α-AMINO-α-PHENYLPROPIONIC ACID

### (*dl*-Alanine, α-phenyl-)

$$C_6H_5COCH_3 + NaCN + NH_4Cl \rightarrow C_6H_5C(CH_3)(NH_2)CN + H_2O + NaCl$$

$$C_6H_5C(CH_3)(NH_2)CN + H_2O + HCl \xrightarrow{\text{cold}} C_6H_5C(CH_3)(NH_3Cl)CONH_2$$

$$C_6H_5C(CH_3)(NH_3Cl)CONH_2 + H_2O + HCl \xrightarrow{\text{hot}} C_6H_5C(CH_3)(NH_3Cl)CO_2H + NH_4Cl$$

$$C_6H_5C(CH_3)(NH_3Cl)CO_2H + C_5H_5N \rightarrow C_6H_5C(CH_3)(NH_2)CO_2H + C_5H_5NHCl$$

Submitted by ROBERT E. STEIGER.
Checked by R. L. SHRINER and S. P. ROWLAND.

### 1. Procedure

In a 2-l. round-bottomed flask are placed, in the order mentioned, 50 g. (1 mole) of 98% sodium cyanide in 100 ml. of water, 58.9 g. (1.1 moles) of ammonium chloride in 140 ml. of lukewarm water (about 35°), and 134 ml. (2 moles) of aqueous ammonia (sp. gr. 0.90). The mixture is shaken while 120 g. (1 mole) of acetophenone in 300 ml. of 95% ethyl alcohol is added. The flask is stoppered with a rubber stopper, which is wired in place (Note 1), and is then immersed in a water bath maintained at 60°. The flask is shaken from time to time, and a homogeneous solution results within half an hour. The reaction mixture is heated for 5 hours at 60°, then well cooled in an ice-water mixture, and poured, with precautions (under a well-ventilated hood), into a 5-l. round-bottomed flask which is immersed up to the neck in an ice-water mixture and which contains 800 ml. of concentrated hydrochloric acid (sp. gr. 1.18–1.19). The reaction flask is rinsed with two 25-ml. portions of water, which are added to the hydrochloric acid solution. The solution of the aminonitrile is satu-

rated at 0–5° with dry hydrogen chloride (Note 2) and is then set aside overnight in the ice-water bath, which is allowed to melt and come to the temperature of the room. The mixture of solid and liquid material is diluted with 1 l. of water and boiled vigorously for 2.5 hours under a reflux condenser in a well-ventilated hood (Note 3). The dark hydrolysate is concentrated under reduced pressure to remove the acetophenone and other volatile impurities. The solution is finally transferred to a 10-in. evaporating dish and is stirred occasionally while it is evaporated almost to dryness. Once a heavy deposit of inorganic salts has formed, very little bumping occurs. The solid residue is evaporated on a water bath twice with 100-ml. portions of water in order to remove as much hydrochloric acid as possible. The residue is crushed, and 600 ml. of absolute ethyl alcohol is added. The suspension is warmed for a short time on a steam bath; it is shaken thoroughly and then chilled in an ice-water mixture. The inorganic salts are removed by filtration through a 15-cm. Büchner funnel, and the cake is washed with small portions of absolute alcohol until 600 ml. has been used. The combined filtrates and washings are placed in a 3-l. beaker, and pyridine is added while the mixture is stirred by hand with a thick glass rod. The addition of pyridine is continued until the solution is nearly neutral to Congo red paper, and then an additional 50 ml. is added; the total amount of pyridine required is 80–100 ml. (Note 4).

The resulting rather stiff paste is chilled in an ice-water mixture for 1 hour. The solid is collected on a 15-cm. Büchner funnel and washed with 25-ml. portions of absolute ethyl alcohol until it is white and until the filtrate becomes colorless (100–200 ml. of alcohol is required). The fluffy material, after it is dried in a vacuum desiccator over flake sodium hydroxide, weighs 66 g. (40%).

The amino acid contains a small amount of ammonium chloride, which can be removed by dissolving the product in 21 times its weight of water and precipitating it by the addition of 42 times its weight of absolute ethyl alcohol (Note 5). The mixture is allowed to stand overnight in a refrigerator. The amino acid

is collected on a Büchner funnel and washed with an ethyl alcohol-water mixture containing 80% by weight of ethyl alcohol. The amino acid is dried in a vacuum desiccator over flake sodium hydroxide. The recovery is about 70% (Note 6).

## 2. Notes

1. A flask fitted with a ground-glass stopper is convenient for carrying out this step. The ground-glass stopper should be slightly lubricated with stopcock grease. It must be firmly secured in place by means of adhesive tape, as some pressure develops when the reaction mixture is heated.

2. From 500 to 600 g. of dry hydrogen chloride gas is required. Since this gas is very rapidly absorbed, a high-speed generator can be used.

3. The hydrolysis of the aminonitrile must be carried out under a good hood. The top of the reflux condenser should be connected with the ventilating pipe by means of a piece of glass tubing.

4. The minimum amount of pyridine necessary is determined by the amount of hydrochloric acid remaining in the residue.

5. The material does not readily become wet in contact with water, and it dissolves very slowly. The finely powdered material is best suspended in a large excess of water, e.g., about 30 times its weight. The suspension is boiled under a reflux condenser and frequently shaken until the solid is dissolved. The excess water is then boiled off at atmospheric pressure until a solution of the amino acid in 21 times its weight of water is obtained. The solution is then cooled and treated with absolute alcohol.

6. The amino acid does not have a sharp melting point. It sublimes with decomposition at about 265–270°.

## 3. Methods of Preparation

$\alpha$-Amino-$\alpha$-phenylpropionitrile has been prepared by heating acetophenone cyanohydrin for 6 to 8 hours in a closed vessel with

1 equivalent of ethyl alcoholic ammonia at 70°;[1,2] and by heating acetophenone for 4 hours in a closed vessel with an ethyl alcoholic solution of ammonium cyanide to 80°.[3] α-Amino-α-phenylpropionitrile has been hydrolyzed by the action of, first, fuming hydrochloric acid at room temperature, and then dilute hydrochloric acid at boiling temperature, in the presence of some ethyl alcohol. This procedure gives a good yield of the amino acid hydrochloride. The amino acid has usually been liberated from its hydrochloride by means of ammonium hydroxide.[1,2,3] The process of isolating the amino acid by treating an alcoholic solution of its hydrochloride with pyridine is essentially the same as that developed for the preparation of glycine[4] and of α-amino-isobutyric acid.[5]

## 4-AMINO-1,2,4-TRIAZOLE

### (1,3,4-Triazole, 1-amino-)

$$HCO_2C_2H_5 + NH_2NH_2 \cdot H_2O \rightarrow HCONHNH_2 + C_2H_5OH + H_2O$$

$$2HCONHNH_2 \xrightarrow{\text{heat}} NH_2N\left\langle \begin{array}{l} CH{=}N \\ \qquad | \\ CH{=}N \end{array} \right. + 2H_2O$$

Submitted by C. F. H. ALLEN and ALAN BELL.
Checked by W. E. BACHMANN and G. DANA JOHNSON.

### 1. Procedure

In a 1-l. round-bottomed flask, equipped with an efficient water condenser, are placed 148 g. (2 moles) of ethyl formate (b.p. 52–53°) and 150 ml. of 95% ethanol. One hundred and twenty grams (2 moles) of 85% hydrazine hydrate is added

[1] Tiemann and Köhler, *Ber.*, **14**, 1981 (1881).
[2] McKenzie and Clough, *J. Chem. Soc.*, **101**, 395 (1912).
[3] Jawelow, *Ber.*, **39**, 1195, 1197 (1906).
[4] Clarke and Taylor, *Org. Syntheses*, **4**, 31 (1925); Coll. Vol. **I**, 298 (1941).
[5] Clarke and Bean, *Org. Syntheses*, **11**, 4 (1931); Coll. Vol. **2**, 29 (1942).

cautiously to this solution (Note 1) with shaking over a period of 10 minutes. After the reaction has subsided, the solution is refluxed on a steam bath for 18 hours. The bulk of the water and alcohol is now removed by evaporation under reduced pressure until the volume in the flask is about 150 ml. The resulting syrup, crude formhydrazide, is heated under atmospheric pressure for 3 hours, during which time the temperature of the bath is raised from 150° to 200°. After cooling to about 100°, the oil is taken up in 50 ml. of 95% ethanol, and 5 g. of Norite is added. The filtered solution is then diluted with 75 ml. of ether and placed in an icebox to cool. The crystalline product is filtered, washed with 50 ml. of 1 : 2 alcohol-ether, and dried. The yield of aminotriazole, melting at 77–78°, is 55–60 g. (65–71%) (Note 2). If a purer product is desired, the crude, washed material may be recrystallized, using 2 ml. of warm 95% ethanol per gram of compound followed by addition of 2.5 ml. of ether, and chilling. The melting point of the purified product is 81–82°.

The residual amine in the filtrate may be isolated in the form of the hydrochloride. The combined solutions are evaporated on a steam bath, 50 ml. of concentrated hydrochloric acid is added, and heating is continued for 2 hours. On cooling, the syrupy solution crystallizes. It is triturated with 50 ml. of ethanol, and the 4-amino-1,2,4-triazole hydrochloride is filtered, washed with a little ethanol, and dried. The yield of the hydrochloride is 10–18 g. (8–15%); the salt melts at 147–148° and may be recrystallized from 95% ethanol, using 10 ml. per gram; the melting point is thus raised to 151–152°.

## 2. Notes

1. The reaction is very vigorous, but, if the hydrazine hydrate is added carefully, no difficulty of control is encountered.

2. The combined yield of base and hydrochloride is always about 80–81%. When the amount of base is low, that of the hydrochloride is high.

### 3. Methods of Preparation

4-Amino-1,2,4-triazole has been obtained from orthoformic ester and hydrazine hydrate in a sealed tube at 120°;[1] by heating formylhydrazine at 150–210°;[2,3,4] by heating N,N′-diformylhydrazine at 160°;[5] by decarboxylation of 4-amino-1,2,4-triazoldicarboxylic acid;[6] by fusion of 1,2-dihydro-1,2,4,5-tetrazine;[6] and by heating 1,2-dihydro-1,2,4,5-tetrazinedicarboxylic acid above its melting point.[4,6,7]

## BENZOYL CYANIDE

$$C_6H_5COCl + CuCN \rightarrow C_6H_5COCN + CuCl$$

Submitted by T. S. Oakwood and C. A. Weisgerber.
Checked by R. L. Shriner and Charles R. Russell.

### 1. Procedure

In a 500-ml. distilling flask (Note 1) fitted with a thermometer extending to within 0.5 in. of the bottom are placed 110 g. (1.2 moles) of cuprous cyanide (Note 2) and 143 g. (118 ml., 1.02 moles) of purified benzoyl chloride (Note 3). The flask is shaken to moisten almost all the cuprous cyanide and is placed in an oil bath (Note 4) which has been previously heated to 145–150°. The temperature of the bath is raised to 220–230° and maintained between these limits for 1.5 hours. During the heating the flask is frequently removed from the bath (about every 15 minutes) and the contents are thoroughly mixed by vigorous shaking (Note 5). At the end of the 1.5 hours the flask

[1] Stolle, *J. prakt. Chem.*, (2) **68**, 467 (1903).
[2] Ruhemann and Stapleton, *J. Chem. Soc.*, **75**, 1132 (1899).
[3] Ruhemann and Merriman, *J. Chem. Soc.*, **87**, 1772 (1905).
[4] Hantzsch and Silberrad, *Ber.*, **33**, 85 (1900).
[5] Pellizzari, *Atti accad. Lincei*, (5) **8** (I), 331 (*Chem. Zentr.*, **1899**, I, 1240); *Gazz. chim. ital.*, **39** (I), 530 (1909).
[6] Curtius, Darapsky, and Müller, *Ber.*, **40**, 835, 1194 (1907).
[7] Curtius and Lang, *J. prakt. Chem.*, (2) **38**, 549 (1888).

is connected with an air-cooled condenser set for downward distillation. The temperature of the bath is slowly raised to 305–310°, and distillation is continued until no more product comes over (Note 6). About 100–112 g. of crude benzoyl cyanide boiling at 207–218°/745 mm. is obtained.

The crude benzoyl cyanide is purified by fractional distillation through a column (Note 7). The low-boiling material is taken off at a reflux ratio of 25–30 to 1 until the temperature reaches 208°; about 15 g. is collected. The benzoyl cyanide is collected at a reflux ratio of 1 to 1 at a temperature of 208–209°/745 mm. (bath temperature 260–280°). The distillate solidifies to colorless crystals which melt at 32–33°; the product weighs 80–86 g. (60–65%).

## 2. Notes

1. It is advisable to wrap the neck of the flask with asbestos paper or asbestos tape.

2. The cuprous cyanide is dried at 110° for 3 hours before use.

3. The commercial grade of benzoyl chloride may be purified as follows: 300 ml. (363 g.) of benzoyl chloride in 200 ml. of benzene is washed with two 100-ml. portions of cold 5% sodium bicarbonate solution. The benzene layer is separated, dried over calcium chloride, and distilled. After all the benzene has distilled, pure benzoyl chloride boiling at 196.8° (corr.)/745 mm. is collected. The recovery is 225 g.

4. Hydrogenated cottonseed oil, "Coto Flakes," obtainable from the Procter and Gamble Company, Cincinnati, Ohio, is suitable for the bath. A Wood's metal bath may also be used.

5. Upon addition of the benzoyl chloride to the cuprous cyanide thorough mixing by shaking is impossible. After the mixture is heated for about 30 minutes, the solid becomes granular and mixing is easily effected.

6. The distillate should be collected in the 200-ml. round-bottomed flask which is used in the subsequent fractionation. The distillation takes about an hour. The cake of copper salts in the flask is best removed by digestion with concentrated ammonium hydroxide solution.

7. The fractionating column was of the Whitmore-Lux type [1] and had about 14 theoretical plates. The packed section was 37 by 1.1 cm. (o.d.) and was packed with $\frac{3}{32}$-in. single-turn glass helices. The distilling flask was a 200-ml. round-bottomed flask. A metal bath or the oil bath described in Note 4 may be used for heating.

### 3. Methods of Preparation

Benzoyl cyanide can be prepared by the thermal decomposition of ω-isonitrosoacetophenone,[2] from silver cyanide and benzoyl chloride,[3] from anhydrous hydrogen cyanide and benzoyl chloride in the presence of pyridine,[4] and by the thermal decomposition of phenylchloronitrocyanomethane.[5,6]

## BENZOYLFORMIC ACID

### (Glyoxylic acid, phenyl)

$$C_6H_5COCN + 2H_2O + HCl \rightarrow C_6H_5COCO_2H + NH_4Cl$$

Submitted by T. S. Oakwood and C. A. Weisgerber.
Checked by R. L. Shriner and Charles R. Russell.

### 1. Procedure

In a 1-l. flask are placed 50 g. (0.38 mole) of benzoyl cyanide (p. 14) and 500 ml. of concentrated hydrochloric acid (sp. gr. 1.18). The mixture is shaken occasionally until the solid is dissolved completely and is then allowed to stand at room temperature for 5 days (Note 1). At the end of this time the clear yellow

[1] Whitmore and Lux, *J. Am. Chem. Soc.*, **54**, 3451 (1932).
[2] Claisen and Manasse, *Ber.*, **20**, 2195 (1887).
[3] Nef, *Ann.*, **287**, 307 (1895).
[4] Claisen, *Ber.*, **31**, 1024 (1898).
[5] Wislicenus and Shafer, *Ber.*, **41**, 4170 (1908).
[6] Staudinger and Kon, *Ann.*, **384**, 115 (1911).

solution is poured into 2 l. of water and extracted with one 400-ml. portion and three 250-ml. portions of ether. The ether is removed by distillation from a steam bath, and the residual oil is placed in a vacuum desiccator containing phosphorus pentoxide and solid sodium hydroxide and allowed to remain there until dry (Note 2). The yield of crude solid acid melting from 57° to 64° is about 55–56 g. (96–98%). The crude acid is dissolved in 750 ml. of hot carbon tetrachloride, and 2 g. of Norite is added (Note 3). The solution is filtered and allowed to cool to room temperature and then cooled in an ice-water mixture until crystallization is complete. The solid acid is filtered with suction, and the solvent remaining on the crystals is removed by placing the product in a vacuum desiccator for about 2 days. The yield of slightly yellow benzoylformic acid melting at 64–66° is 42–44 g. (73–77%) (Note 4).

## 2. Notes

1. With occasional shaking about a day is necessary for complete solution of the solid benzoyl cyanide. A yellow oil separates which dissolves on shaking. At the end of this time some ammonium chloride occasionally separates.
2. If the oil does not crystallize it is cooled in an ice-water mixture until solidification is complete. The solid is returned to the desiccator for complete drying. The desiccator must be evacuated slowly or spattering will take place.
3. If decolorizing carbon is not used, the acid tends to separate as an oil which solidifies on cooling.
4. Titration with standard sodium hydroxide solution showed the acid to be about 99% pure.

## 3. Methods of Preparation

Benzoylformic acid can be prepared by the oxidation of acetophenone with potassium permanganate in alkaline solution,[1] by the oxidation of mandelic acid with potassium perman-

[1] Claus and Neukranz, *J. prakt. Chem.*, (2) **44**, 80 (1891).

ganate in alkaline solution,[2,3] and by the hydrolysis of benzoyl cyanide with concentrated hydrochloric acid.[4]

## *tert.*-BUTYL ACETATE

### (Acetic acid, *tert.*-butyl ester)

### ACETIC ANHYDRIDE METHOD

$$(CH_3)_3COH + (CH_3CO)_2O \xrightarrow{ZnCl_2} CH_3CO_2C(CH_3)_3 + CH_3CO_2H$$

Submitted by Robert H. Baker and Frederick G. Bordwell.
Checked by R. L. Shriner and Fred W. Neumann.

### 1. Procedure

In a 1-l. flask equipped with a reflux condenser and drying tube are placed 200 ml. (2.1 moles) of *tert.*-butyl alcohol (Note 1), 200 ml. (2.1 moles) of acetic anhydride, and 0.5 g. of anhydrous zinc chloride. After thorough shaking, the mixture is slowly heated to reflux temperature, maintained at gentle refluxing for 2 hours, and then cooled. The reflux condenser is replaced by a 20-cm. Vigreux column through which the mixture is distilled up to a temperature of 110°. The crude distillate, weighing 200-250 g., is washed with two 50-ml. portions of water, then with 50-ml. portions of 10% potassium carbonate until the ester layer is neutral to litmus; the product is finally dried over anhydrous potassium carbonate (about 20 g.).

After removal of the drying agent, the ester is fractionally distilled through an efficient fractionating column (Note 2). A fore-run of 21–37 g. is collected up to a temperature of 95°. The pure ester distils between 95° and 96° and amounts to 129–148 g. (53–60%) (Note 3).

[2] Acree, *Am. Chem. J.*, **50**, 391 (1913).
[3] *Org. Syntheses* Coll. Vol. **I**, 241 (1941).
[4] Boeseken and Felix, *Rec. trav. chim.*, **40**, 569 (1921).

## 2. Notes

1. Eastman Kodak Company's best grade of *tert.*-butyl alcohol and the Practical grade of acetic anhydride are satisfactory. If these are not available, the alcohol should be dried over quicklime and distilled, and the acetic anhydride should be redistilled also.

2. The fractionating column may be a 16-plate Stedman column or a 30-cm. Carborundum-packed column.[1]

3. The corrected boiling point of the ester is given as 97.9°.[2]

### ACETYL CHLORIDE METHOD

$$(CH_3)_3COH + CH_3COCl + C_6H_5N(CH_3)_2 \rightarrow CH_3CO_2C(CH_3)_3 + C_6H_5N(CH_3)_2 \cdot HCl$$

Submitted by C. R. Hauser, B. E. Hudson, B. Abramovitch, and J. C. Shivers.
Checked by R. L. Shriner and Fred W. Neumann.

## 1. Procedure

In a 2-l. flask equipped with a reflux condenser, mercury-sealed stirrer, and a dropping funnel are placed 147 ml. (114 g., 1.5 moles) of *tert.*-butyl alcohol (Note 1), 212 ml. (202 g., 1.67 moles) of dimethylaniline, and 200 ml. of dry ether. The solution is heated to refluxing, and 113 ml. (124 g., 1.58 moles) of acetyl chloride is run into the stirred solution at such a rate that moderate refluxing continues after the source of heat is removed. When approximately two-thirds of the acetyl chloride has been added, dimethylaniline hydrochloride begins to crystallize and the mixture refluxes very vigorously. An ice bath is applied immediately, and, after refluxing ceases, the remainder of the acetyl chloride is added. Finally, the mixture is heated for 1 hour on a water bath. The mixture is cooled to room tempera-

[1] *Org. Syntheses*, **20**, 96 (1940).

[2] Bryant and Smith, *J. Am. Chem. Soc.*, **58**, 1016 (1936).

ture, approximately 200 ml. of water is added, and stirring is continued until all the solid material dissolves. The ether layer is separated and extracted with 50-ml. portions of cold 10% sulfuric acid until the extract does not become cloudy when made alkaline with sodium hydroxide. After a final washing with 25 ml. of saturated sodium bicarbonate solution, the ether solution is dried by shaking it with 10 g. of anhydrous sodium sulfate. The solution is decanted and allowed to stand over 10 g. of Drierite overnight. The solution is filtered, and the ether is removed by distillation through a good fractionating column (Note 2). The residue is fractionally distilled, and 110–119 g. (63–68%) of *tert.*-butyl acetate boiling at 95–98° is obtained (Note 2). Most of the ester boils at 97.0–97.5° (Note 3).

## 2. Notes

1. All reactants should be pure and anhydrous. The *tert.*-butyl alcohol should be dried over quicklime and the dimethylaniline redistilled. Reagent grade acetyl chloride should be employed.

2. Either a 30-cm. Carborundum-packed column [1] or a 30-cm. Widmer column may be used. The pure ester was collected over a range of 94.5–95.5°.

3. The submitters report that the following *tert.*-butyl esters have been prepared in a similar manner. Eastman Kodak Company chemicals were used.

(*a*) *tert.*-Butyl propionate. From 221 ml. (171 g., 2.31 moles) of *tert.*-butyl alcohol, 318 ml. (303 g., 2.5 moles) of dimethylaniline, and 206 ml. (220 g., 2.38 moles) of propionyl chloride, refluxed for 3 hours, there was obtained 184 g. (61.4%) of *tert.*-butyl propionate, b.p. 117–118.5°; most of the product boiled at 118.0–118.5°.

(*b*) *tert.*-Butyl isobutyrate. From 94.5 ml. (73.4 g., 0.99 mole) of *tert.*-butyl alcohol, 127 ml. (121 g., 1 mole) of dimethylaniline in 200 ml. of ether, and 105 ml. (108 g., 1 mole) of isobutyryl chloride in 50 ml. of ether, after standing for 15 hours at room temperature, the ether being distilled, and the residue

heated for 5 hours on a water bath, there was obtained 102 g. (71%) of the ester boiling at 127–128.3°.

(*c*) *tert.*-Butyl isovalerate. From 121.4 g. (1.64 moles) of *tert.*-butyl alcohol, 198.5 g. (1.64 moles) of dimethylaniline, and 200.7 g. (1.66 moles) of isovaleryl chloride, after standing overnight, the ether being distilled, and the residue heated for 5 hours on a water bath, there was obtained 67.3 g. (26%) of *tert.*-butyl isovalerate boiling at 154–157°.

(*d*) *tert.*-Butyl cinnamate. The cinnamoyl chloride from 100 g. (0.675 mole) of cinnamic acid and 400 g. (3.37 moles) of thionyl chloride was treated with 64 ml. (49.5 g., 0.67 mole) of *tert.*-butyl alcohol and 90 ml. (86.0 g., 0.71 mole) of dimethylaniline. The mixture was refluxed 12 hours and then allowed to stand 12 hours at room temperature. Distillation furnished 78.8 g. (58%) of *tert.*-butyl cinnamate boiling at 144°/8 mm.

(*e*) *tert.*-Butyl chloroacetate (submitted by Robert H. Baker). Thirty-five and four-tenths milliliters (0.4 mole) of *tert.*-butyl alcohol was added over a period of 10 minutes to a mixture of 30.6 ml. (0.4 mole) of chloroacetyl chloride and 50 ml. (0.4 mole) of dimethylaniline, care being taken to keep the temperature below 30°. After standing 45 minutes at room temperature, the mixture was poured into water and worked up in the usual way. The ester was fractionated in a 6-in. Widmer column. The yield was 38 g. (63%) of ester which boiled at 48–49°/11 mm.; $N_D^{20}$ 1.4259–1.4260.

### 3. Methods of Preparation

*tert.*-Butyl acetate has been prepared from the alcohol and acetyl chloride in the presence of pyridine,[2] dimethylaniline,[3] or magnesium;[4] from the alcohol and acetic anhydride in the presence of anhydrous zinc chloride,[3] a small amount of zinc dust,[3] or anhydrous sodium acetate.[5] The methods described above are adapted from the directions of Norris and Rigby.[3]

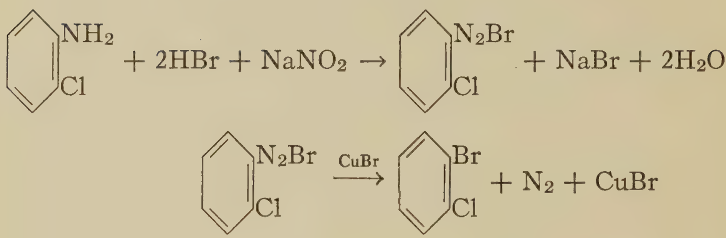
[3] Norris and Rigby, *J. Am. Chem. Soc.*, **54**, 2098 (1932).

[4] Spassow, *Org. Syntheses*, **20**, 21 (1940).

[5] Tronow and Sribgatullin, *Ber.*, **62**, 2850 (1929).

# o-CHLOROBROMOBENZENE

## (Benzene, 1-bromo-2-chloro-)



Submitted by Jonathan L. Hartwell.
Checked by H. R. Snyder and Zeno Wicks, Jr.

### 1. Procedure

A mixture of 127.5 g. (1 mole) of a good commercial grade of *o*-chloroaniline and 300 ml. (2.5 moles) of 48% hydrobromic acid (Note 1) in a 2-l. flask set in an ice bath is cooled to 0° by the addition of ice. A solution of 70 g. (1 mole) of sodium nitrite in 125 ml. of water is added rapidly, with stirring, the temperature being kept below 10° by the addition of small pieces of ice. When only about 5 ml. of the sodium nitrite solution remains, further additions are made cautiously until an excess of nitrous acid remains after the last addition (Note 2).

In the meantime, a mixture of 79 g. (0.55 mole) of cuprous bromide (Note 3) and 80 ml. (0.6 mole) of 48% hydrobromic acid (Note 1) is heated to boiling in a 5-l. round-bottomed three-necked flask, equipped with a condenser set for distillation and provided with a 2-l. receiving flask, a steam inlet tube closed by a screw clamp, and a separatory funnel. About one-fourth of the diazonium solution is transferred to the separatory funnel, without filtration, and immediately run into the cuprous bromide-hydrobromic acid solution, which is kept boiling over a free flame, at such a rate that boiling is continuous. When the separatory funnel is nearly empty a further portion of the cold

diazonium solution is transferred to it without interrupting the addition. All the diazonium solution is added in this way over a period of about 30 minutes, during which time much of the product steam-distils. When the addition is complete, the stopcock in the separatory funnel is closed, the screw clamp in the steam line is opened, and a vigorous current of steam is passed through the mixture until no more organic material distils. About 1–1.5 l. of distillate is collected.

The heavy organic layer is separated from the distillate and washed with 10-ml. portions of concentrated sulfuric acid until the acid becomes only slightly colored during the washings; four washings usually suffice. The oil is then washed with one 100-ml. portion of water, two 50-ml. portions of 5% aqueous sodium hydroxide, and finally with one 100-ml. portion of water. The product is dried over about 3 g. of calcium chloride and distilled from a 250-ml. distilling flask. The yield of pure, colorless *o*-chlorobromobenzene, boiling at 199–201°/742 mm., is 170–183 g. (89–95%) (Notes 4 and 5).

## 2. Notes

1. When 40% hydrobromic acid is used in both the diazotization and Sandmeyer reaction the yield is only about 75%.

2. Free nitrous acid causes an *immediate* blue color at the point of contact with starch-iodide test paper. A delayed color or a color around the periphery of the wetted area is of no significance. At all times there must be an excess of mineral acid (blue color on Congo paper).

3. The submitter used commercial cuprous bromide. The checkers prepared cuprous bromide by dissolving 600 g. (2.4 moles) of commercial copper sulfate crystals and 350 g. (3.4 moles) of sodium bromide in 2 l. of warm water; the solution was stirred while 151 g. (1.2 moles) of solid sodium sulfite was added over a period of 10 minutes. Occasionally a little more sodium sulfite was required to discharge the blue color. The mixture was cooled, and the solid collected on an 8-in. Büchner funnel, washed once with water, pressed nearly dry, and then dried in

the air overnight. The yield of cuprous bromide was 320 g. (93%).

4. Runs 3 times this size give proportional yields.

5. The checkers have prepared the following bromides by the same procedure: *m*-chlorobromobenzene (b.p. 191–194°) from *m*-chloroaniline in 91–94% yields; *m*-dibromobenzene (b.p. 215–217°) from *m*-bromoaniline in 80–87% yields; and *o*-bromoanisole (b.p. 114–116°/29 mm.) from *o*-anisidine in 88–93% yields. In the preparation of *o*-bromoanisole the washing with sulfuric acid was omitted.

## 3. Methods of Preparation

*o*-Chlorobromobenzene has been prepared by the diazotization of *o*-bromoaniline followed by replacement of the diazonium group by chlorine;[1] by the elimination of the amino group from 3-chloro-4-bromoaniline;[2] by the chlorination of bromobenzene in the presence of thallous chloride,[3] aluminum chloride,[4] or ferric chloride;[4] by the bromination of chlorobenzene without a catalyst[5] or in the presence of aluminum,[4] iron,[4] or ferric bromide;[5] by the diazotization of *o*-chloroaniline followed by replacement of the diazonium group with bromine;[4,6] and from *o*-chlorophenylmercuric chloride by the action of bromine.[7]

[1] Dobbie and Marsden, *J. Chem. Soc.*, **73**, 254 (1898).
[2] Wheeler and Valentine, *Am. Chem. J.*, **22**, 266 (1899).
[3] Thomas, *Compt. rend.*, **144**, 33 (1907).
[4] Vander Linden, *Rec. trav. chim.*, **30**, 305 (1911).
[5] Van Loon and Wibaut, *Rec. trav. chim.*, **56**, 815 (1937).
[6] Narbutt, *Ber.*, **52**, 1028 (1919).
[7] Hanke, *J. Am. Chem. Soc.*, **45**, 1321 (1923).

## ω-CHLOROISONITROSOACETOPHENONE

### (Glyoxylyl chloride, phenyl-, oxime)

$$C_6H_5COCH_2Cl + n\text{-}C_4H_9ONO \xrightarrow{HCl} C_6H_5COC(NOH)Cl + n\text{-}C_4H_9OH$$

Submitted by NATHAN LEVIN and WALTER H. HARTUNG.
Checked by C. F. H. ALLEN and J. VAN ALLAN.

### 1. Procedure

A 500-ml. three-necked round-bottomed flask is provided with a small dropping funnel, a sealed mechanical stirrer, a reflux condenser connected to a gas-absorption trap, and a hydrogen chloride delivery tube which extends to the bottom of the flask.

In the reaction flask are placed 15.4 g. (0.1 mole) of phenacyl chloride (Note 1) and 100 ml. of dry ether. The stirrer is started, and, after the solid has dissolved, anhydrous hydrogen chloride (Note 2) is introduced at the rate of 2–3 bubbles per second. Ten and three-tenth grams (11.8 ml., 0.1 mole) of freshly distilled *n*-butyl nitrite [1] (Note 3) is then admitted from the dropping funnel in 0.5- to 1-ml. portions. After addition of the first portion of nitrite the reaction mixture becomes orange-brown, and after several minutes, light yellow; at this point a second portion of nitrite is added and a similar color change takes place, whereupon a third portion is added; further additions are made until all the butyl nitrite has been added. The reaction mixture warms up, and the ether begins to reflux gently (Note 4). After all the nitrite has been added (about 30 minutes is required), stirring and addition of hydrogen chloride are continued an additional 15 minutes. At this point, the solution will have practically ceased boiling and will have assumed an orange color.

[1] *Org. Syntheses* Coll. Vol. 2, 108 (1943).

The reaction mixture is allowed to stand for 1 to 2 hours (or overnight, if more convenient); after this interval the solution will have assumed a clear, pale yellow color. The condenser is then set for downward distillation, stirring is resumed, and the solvent is removed by distillation from a steam bath (Note 5). After nearly all the ether has been removed, the distillation is continued under reduced pressure (40–50 mm.) until no further appearance of crystals is noted. The residue, which consists of yellow crystals of the crude product, is then allowed to stand until dry in a vacuum desiccator which contains concentrated sulfuric acid, soda lime, and anhydrous calcium chloride (Note 6).

The dried product is then recrystallized from 30–35 ml. of a 1 : 3 mixture of boiling benzene and carbon tetrachloride (Note 7). The yield of snow-white crystals is 15–15.7 g. (82–86%); the recrystallized product melts at 131–132° and is sufficiently pure for synthetic purposes. A second recrystallization gives a product which melts at 132–133° (Notes 8 and 9).

## 2. Notes

1. Commercial phenacyl chloride may be used; if unavailable the chloride may be prepared in 85–88% yield by a Friedel-Crafts reaction, using 234 g. (265 ml., 3 moles) of dry benzene and 79.5 g. (53 ml., 0.70 mole) of chloroacetyl chloride, in the presence of 103 g. (0.77 mole) of powdered anhydrous aluminum chloride; the product distils at 120–125°/4 mm. and melts at 56–57°. *Phenacyl chloride is a strong lachrymator and vesicant; it should be handled with care.*

2. Hydrogen chloride is now available in cylinders.

3. Any alkyl nitrite may be employed. The submitters preferred the use of isopropyl nitrite, since the low boiling point of the isopropyl alcohol formed facilitates its removal.

Isopropyl nitrite may be prepared according to the procedure given for *n*-butyl nitrite.[1]

A mixture of 147 g. (80 ml., 1.5 moles) of concentrated sulfuric acid (sp. gr. 1.84), 60 ml. of water, and 180 g. (230 ml., 3 moles) of 97% isopropyl alcohol, previously cooled to 0°, is

added to a solution of 227.7 g. (3.3 moles) of 97% sodium nitrite in 1 l. of water, cooled to −5°. About 2 hours is required for the addition of the alcohol solution, during which time the temperature of the reaction mixture is maintained at −2° to 0°. The product may be isolated and purified as described under butyl nitrite. After drying over 15–20 g. of anhydrous sodium sulfate, the nitrite is distilled from a steam bath using a 20-cm. column. Practically all the isopropyl nitrite distils at 39–40°/745 mm. as a pale yellow oil; the yield of product is 191 g. (71.4%). Isopropyl nitrite, when stored in a refrigerator, has been found to be much more stable than butyl nitrite.

The checkers used commercially available *n*-butyl nitrite and experienced no difficulty in removing the *n*-butyl alcohol.

4. The rate of stirring must be kept fairly constant since an abrupt increase in speed may cause the ether to reflux at an undesirably rapid rate. The rate of addition of the nitrite is also governed by the rate of the refluxing.

5. The recovered ether may be employed without purification as the solvent in a subsequent run.

6. ω-Chloroisonitrosoacetophenone is extremely soluble in butanol, hence the alcohol should be removed as completely as possible before the crude product is recrystallized.

7. This is most conveniently done by dissolving the chloride in the benzene and then diluting.

8. This procedure works equally well in 0.5-mole runs.

9. This procedure, with minor changes, may be applied to various nuclear-substituted phenacyl chlorides. The yields vary from 74 to 92%.[2,3]

### 3. Methods of Preparation

The above procedure[2] is modeled after that described for the nitrosation of arylethyl ketones.[4,5] ω-Chloroisonitrosoacetophenone has been prepared by the chlorination of isonitro-

[2] Levin, Thesis, University of Maryland, 1941.

[3] Levin and Hartung, *J. Org. Chem.*, **7**, 408 (1942).

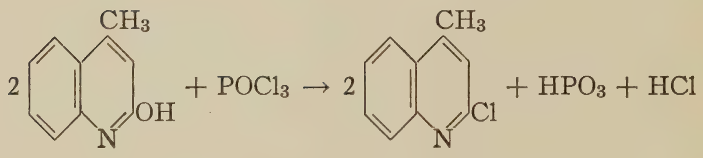
[4] Hartung and Munch, *J. Am. Chem. Soc.*, **51**, 2264 (1929).

[5] Hartung and Crosby, *Org. Syntheses* Coll. Vol. **2**, 363 (1942).

soacetophenone;[6,7,8] by treating the ammonium salt of ω-nitroacetophenone with anhydrous hydrogen chloride,[9] or by refluxing ω-nitroacetophenone with dilute alcoholic hydrogen chloride;[10] and by the nitrosochlorination of acetophenone with nitrosyl chloride.[11] The isolation of small quantities of ω-chloroisonitrosoacetophenone from the reaction product obtained by nitrosating acetophenone in the presence of hydrogen chloride has been reported.[12,13]

## 2-CHLOROLEPIDINE

**(Lepidine, 2-chloro-)**



Submitted by C. E. Kaslow and W. M. Lauer.
Checked by C. F. H. Allen and H. W. J. Cressman.

### 1. Procedure

In a 500-ml. flask, to which is attached an air condenser whose open end is protected by absorbent cotton or calcium chloride in a drying tube,[1] are mixed 119 g. (0.75 mole) of 4-methylcarbostyril (p. 68) and 138 g. (82.5 ml., 0.9 mole) of

[6] Claisen and Manasse, *Ann.*, **274**, 95 (1893).
[7] Ponzio and Charrier, *Gazz. chim. ital.*, (2) **37**, 65 (1907).
[8] Ponzio, *Gazz. chim. ital.*, **61**, 946 (1931).
[9] Steinkopf and Jurgens, *J. prakt. Chem.*, (2) **84**, 712 (1911).
[10] Jakubowitsch, *J. prakt. Chem.*, **142**, 46 (1935).
[11] Rheinboldt and Schmitz-Dumont, *Ann.*, **444**, 125 (1925).
[12] Claisen, *Ber.*, **20**, 252 (1887).
[13] Claisen and Manasse, *Ber.*, **22**, 526 (1889).

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2-CHLOROLEPIDINE

[1] *Org. Syntheses*, **20**, 9 (1940).

freshly distilled phosphorus oxychloride. The mixture is maintained at 80–85° in a water bath for about 15 minutes until most of the solid has dissolved, and then it is warmed carefully for an additional 15 minutes on a wire gauze until solution is complete. The hot reaction mixture is poured into 1 l. of water containing 1 kg. of cracked ice.

The 2-chlorolepidine is extracted, using two 750-ml. portions of ether (Note 1). The extract is shaken with two 200-ml. portions of water and then dried over 50 g. of potassium carbonate. After removal of the ether, the residual oil is distilled from a 200-ml. modified Claisen flask.[2] The colorless distillate boils at 132–135°/3 mm. and weighs 118–122 g. (89–92%). The distillate is melted if necessary and poured into 250 ml. of petroleum ether (b.p. 40–50°); the solution is then chilled in a freezing mixture; the crystals are filtered by suction and dried in a vacuum desiccator over paraffin. The snow-white 2-chlorolepidine melts at 58–59° and weighs 114–118 g. (86–89%).

## 2. Note

1. An additional 5–8 g. of slightly colored material can be secured by neutralizing the aqueous solution with 200 g. of sodium carbonate, extracting with 500 ml. of ether, and distilling. The total yield of distilled product then amounts to 125–130 g. (95–97%).

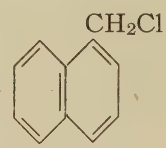
## 3. Methods of Preparation

The preparation described is based on the method of Knorr,[3] recently used by Mikhailov,[4] and Krahler and Burger.[5] 2-Chlorolepidine has also been prepared by the action of benzoyl chloride on 4-methylcarbostyril.[6]

[2] *Org. Syntheses* Coll. Vol. **2**, 18 (1943).
[3] Knorr, *Ann.*, **236**, 98 (1886).
[4] Mikhailov, *J. Gen. Chem.* (*U.S.S.R.*), **6**, 511 (1936) [*C.A.*, **30**, 6372 (1936)].
[5] Krahler and Burger, *J. Am. Chem. Soc.*, **63**, 2368 (1941).
[6] Ellinger and Reisser, *Ber.*, **42**, 3338 (1909).

# 1-CHLOROMETHYLNAPHTHALENE

## (Naphthalene, 1-chloromethyl-)

$C_{10}H_8 + CH_2O + HCl \rightarrow$  $+ H_2O$

Submitted by Oliver Grummitt and Allen Buck.
Checked by C. F. H. Allen and J. Van Allan.

### 1. Procedure

*Caution: Both chloromethylnaphthalene and the by-products are lachrymators and vesicants. Although it is not necessary to work in a hood, precautions should be taken during the handling of the substance and apparatus.*

In a 3-l. three-necked flask, fitted with a reflux condenser and Hershberg stirrer, are placed 256 g. (2 moles) of naphthalene, 110 g. of paraformaldehyde (Note 1), 260 ml. of glacial acetic acid, 165 ml. of 85% phosphoric acid, and 428 g. (362 ml., 4.2 moles) of concentrated hydrochloric acid. This mixture is heated in a water bath at 80–85° and vigorously stirred for 6 hours (Note 2).

After the mixture has been cooled to 15–20° it is transferred to a 2-l. separatory funnel and the crude product is washed first with two 1-l. portions of water cooled to 5–15°, then with 500 ml. of cold 10% potassium carbonate solution, and finally with 500 ml. of cold water. The product is the lower layer in all the washings. After the addition of 200 ml. of ether, the solution is given a preliminary drying by being allowed to stand over 10 g. of anhydrous potassium carbonate, with frequent shaking, for 1 hour. The lower aqueous layer which forms is separated, and the ether solution is again dried over 20 g. of potassium carbonate for 8–10 hours (Notes 3 and 4).

The dried solution is distilled, first at atmospheric pressure to remove most of the solvent, and then under reduced pressure (Note 5). A fore-run of unused naphthalene amounting to 35–40 g. is collected at 90–110°/5 mm. (Note 6). This is followed by 195–204 g. of 1-chloromethylnaphthalene which boils at 128–133°/5 mm. or at 148–153°/14 mm. (74–77% based on naphthalene consumed) (Notes 7 and 8).

## 2. Notes

1. "Trioxymethylene" from the Eastman Kodak Company was used.

2. The level of the water bath should be maintained at the same height as that of the stirred reaction mixture.

3. Both the washing and drying operations must be done very carefully, because the presence of small amounts of water or acid is liable to cause the product to resinify during the final distillation.

4. The checkers added 50 ml. of dry benzene before distilling the solvent to remove traces of water by azeotropic distillation.

5. The use of a clean, dry flask and a moderate rate of distillation help to overcome the tendency of the product to resinify.

6. Care should be taken to prevent clogging of the line by the naphthalene.

7. The oil pump should be protected from acid fumes by means of a trap containing alkali.

8. The residue left after distillation consists mainly of *bis*-(chloromethyl)-naphthalene and di-1-naphthylmethane.

## 3. Methods of Preparation

1-Chloromethylnaphthalene has been made from naphthalene and a variety of reagents: methyl chloromethyl ether;[1] aqueous formaldehyde and hydrogen chloride with or without sulfuric

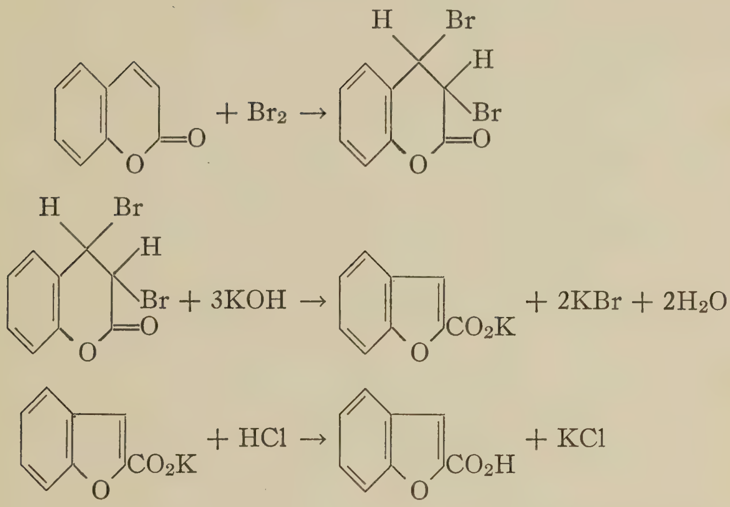
[1] Vavon, Bolle, and Calin, *Bull. soc. chim.*, (5) **6**, 1032 (1939).

acid as a condensing agent;[2,3,4,5,6] and paraformaldehyde and hydrogen chloride or hydrochloric acid.[7,8,9] Catalysts employed have been zinc chloride,[2,10,11,12] aluminum chloride,[11] and phosphoric acid.[13,14,15] Petroleum ether and glacial acetic acid have been used as solvents. The present method is a modification of that described by Cambron.[13]

The chloromethylation of aromatic hydrocarbons has been discussed by Fuson and McKeever.[16]

[2] Blanc, *Bull. soc. chim.*, (4) **33**, 319 (1923).
[3] Jones, U. S. pat. 2,212,099 [*C.A.*, **35**, 462 (1941)].
[4] Coles and Dodds, *J. Am. Chem. Soc.*, **60**, 853 (1938).
[5] Reddelien and Lange, Ger. pat. 508,890 [*C.A.*, **25**, 716 (1931)].
[6] Roblin and Hechenbleikner, U. S. pat. 2,166,554 [*C.A.*, **33**, 8628 (1939)].
[7] Darzens and Levy, *Compt. rend.*, **202**, 74 (1936).
[8] Fieser and Novello, *J. Am. Chem. Soc.*, **62**, 1856 (1940).
[9] Fieser and Gates, *J. Am. Chem. Soc.*, **62**, 2338 (1940).
[10] Ruggli and Burckhardt, *Helv. Chim. Acta*, **23**, 443 (1940).
[11] Tschunkur and Eichler, Ger. pat. 509,149 [*C.A.*, **25**, 711 (1931)].
[12] Anderson and Short, *J. Chem. Soc.*, **1933**, 485.
[13] Cambron, *Can. J. Research*, **17B**, 12 (1939).
[14] Manske and Ledingham, *Can. J. Research*, **17B**, 15 (1939).
[15] Lock and Walter, *Ber.*, **75**, 1158 (1942).
[16] Fuson and McKeever, *Organic Reactions*, Vol. I, p. 63, John Wiley & Sons, 1942.

## COUMARILIC ACID



Submitted by R. C. Fuson, J. Wayne Kneisley, and E. W. Kaiser.
Checked by W. E. Bachmann and G. Dana Johnson.

### 1. Procedure

A. *Coumarin dibromide.* In a 1-l. three-necked flask, equipped with a mechanical stirrer, dropping funnel, and condenser fitted with a trap for hydrogen bromide, are placed 146 g. (1 mole) of coumarin and 200 ml. of chloroform. A solution of 160 g. (1 mole) of bromine in 85 ml. of chloroform is added dropwise to the well-stirred solution of coumarin at room temperature over a period of 3 hours (Note 1). Excess bromine is removed by adding approximately 200 ml. of a 20% solution of sodium sulfite through the dropping funnel. The colorless chloroform layer is separated, washed with two 200-ml. portions of water, and dried over magnesium sulfate (Note 2). After the mixture has stood for only a few minutes (Note 3), the magnesium sulfate is removed by filtration and the solution of the dibromide

is evaporated to 100 ml. in a rapid stream of dry air (Note 4). The coumarin dibromide is collected on a filter, and the mother liquor is evaporated nearly to dryness by an air blast. This mixture is filtered, and the slightly yellow mother liquor is evaporated to dryness. The product of the third evaporation is slightly discolored and is washed with two 15-ml. portions of ether (Note 5). The combined precipitates weigh 215 g. (70%) and melt at 102–105° (Note 6).

B. *Coumarilic acid.* In a 5-l. three-necked flask fitted with a mechanical stirrer and reflux condenser, 450 g. (8 moles) of solid potassium hydroxide is dissolved in 700 ml. of absolute alcohol. The solution is cooled to 15° by immersing the flask in an ice bath, and 215 g. (0.7 mole) of finely divided coumarin dibromide is added in 10- to 15-g. portions to the well-stirred basic solution. The rate of addition is controlled so that the temperature never rises above 20°; the addition requires about 30 minutes. After all the dibromide has been added, the reaction mixture is refluxed, with stirring, for 30 minutes (Note 7). One and a half liters of water is added, and the resulting solution is steam-distilled until 2.5 l. of distillate has been collected (Note 8). The residue is cooled to room temperature by the addition of 1 kg. of cracked ice (Note 9) and is then acidified by the addition of 1.2 l. of 6 *N* hydrochloric acid. The crude coumarilic acid is collected on a filter and stirred with 600 ml. of cold water. The acid is separated from the water by filtration, sucked as dry as possible on the filter, and then crystallized from a mixture of 250 ml. of alcohol and 250 ml. of water (Note 10). The recrystallized coumarilic acid is colorless, weighs 93–100 g. (82–88%) (Note 11), and melts at 190–193°.

## 2. Notes

1. Occasional use of an ice bath is necessary to keep the temperature from rising.

2. If any coumarin dibromide separates before the magnesium sulfate is removed, enough chloroform should be added to dissolve the dibromide.

3. The mixture should be worked up immediately in order to avoid decomposition of the dibromide.

4. The checkers found that considerable decomposition occurred when this procedure was employed, perhaps because it happened to be carried out on a warm humid day; they found it preferable to remove the chloroform by distillation under reduced pressure from a water bath at this step and the succeeding ones. Because of the instability of the dibromide, it is advisable to convert it to coumarilic acid on the day it is made.

5. The first evaporation produces 136 g. of colorless crystals; the second, 63 g.; and the third, 16 g. of ether-washed product.

6. The first crop of crystals melts at 102–105°. The succeeding products melt somewhat lower but are sufficiently pure for the next reaction.

7. The suspension of potassium bromide must be stirred vigorously to avoid bumping.

8. The steam distillation is carried out conveniently by fitting the reaction vessel with a steam inlet tube and a condenser set for downward distillation. The flask should be heated so that the final volume of the distilland is not more than 3 l.

9. A heavy precipitate composed of potassium coumarilate and potassium bromide may appear if the steam distillation has been very efficient. The precipitate dissolves during the addition of hydrochloric acid.

10. The crude acid is dissolved in 250 ml. of boiling absolute alcohol to which has been added 3 g. of Norite; 250 ml. of water, previously heated to 85°, is then added to the filtered solution.

11. The over-all yield, based on the amount of coumarin, is 57–62%.

### 3. Methods of Preparation

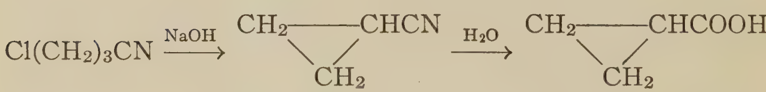
Coumarilic acid has been prepared by treating coumarin dibromide with alcoholic potassium hydroxide and acidifying with hydrochloric acid, a method due essentially to Perkin.[1]

[1] Perkin, *J. Chem. Soc.*, **23**, 368 (1870).

Coumarilic acid has also been prepared by Perkin from 3-chlorocoumarin and from 3-bromocoumarin by the action of alcoholic potassium hydroxide.[2]

Coumarin dibromide has been prepared by the addition of bromine to coumarin in chloroform solution.[1,2]

## CYCLOPROPANECARBOXYLIC ACID



Submitted by Chester M. McCloskey and George H. Coleman.
Checked by C. F. H. Allen and Homer W. J. Cressman.

### 1. Procedure

In a 2-l. three-necked round-bottomed flask surmounted by two large condensers (Notes 1 and 2) are placed 150 g. (3.75 moles) of powdered sodium hydroxide (Note 3) and 103.5 g. (1 mole) of γ-chlorobutyronitrile.[1] The contents of the flask are well mixed by shaking, after which the mixture is heated on a steam bath; a rather vigorous reaction sets in (Note 4). The water formed in the reaction hydrolyzes some of the cyclopropyl cyanide, so that after 1 hour's heating very little liquid is apparent. The hydrolysis of the cyanide is completed by the addition of water in small portions over a period of about 2 hours and subsequent heating; 15-20 ml. of water is added at first, and portions of 60–75 ml. later at intervals of 10-15 minutes until 500 ml. in all has been added. The mixture is then heated for an additional 1.5 hours with occasional stirring; at the end of this time the oily layer will have disappeared.

[2] Perkin, *J. Chem. Soc.*, **24**, 37 (1871).

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CYCLOPROPANECARBOXYLIC ACID

[1] *Org. Syntheses* Coll. Vol. **I**, 156 (1941).

The solution is then cooled in an ice bath and acidified by 200 g. of concentrated sulfuric acid (sp. gr. 1.84) previously mixed with 300 g. of cracked ice. The solution is again cooled in an ice bath. The thick floating layer of cyclopropanecarboxylic acid and various polymers is separated and the cold aqueous solution extracted once with 1 l. of ether, using a stirrer instead of shaking (Note 5). The extract and crude acid are combined and dried over 50 g. of Drierite, and the solvent is removed in a 500-ml. modified Claisen flask [2] on a steam bath. The residue is then distilled under reduced pressure. The yield of acid boiling at 94–95°/26 mm. or 117–118°/75 mm. is 63.5–68 g. (74–79%) (Note 6).

## 2. Notes

1. It is advisable to set up the apparatus in a hood, as small amounts of isocyanide are evolved.
2. The yield is slightly higher if the first vigorous reaction is allowed to take place without external cooling.
3. The commercial flakes are ground in a mortar if powder is not available. The powdered potassium hydroxide on the market can be used equally well.
4. The reaction sets in after about 15 minutes. If potassium hydroxide is used, there is only a 5-minute interval.
5. Since troublesome emulsions tend to form, it is advisable to avoid all vigorous shaking. If the mixture is stirred mechanically for 15 minutes, emulsions are avoided; if formed, they can be broken by treatment with anhydrous sodium sulfate.
6. The submitters have made runs twice this size; the yields were proportional to those given above.

## 3. Methods of Preparation

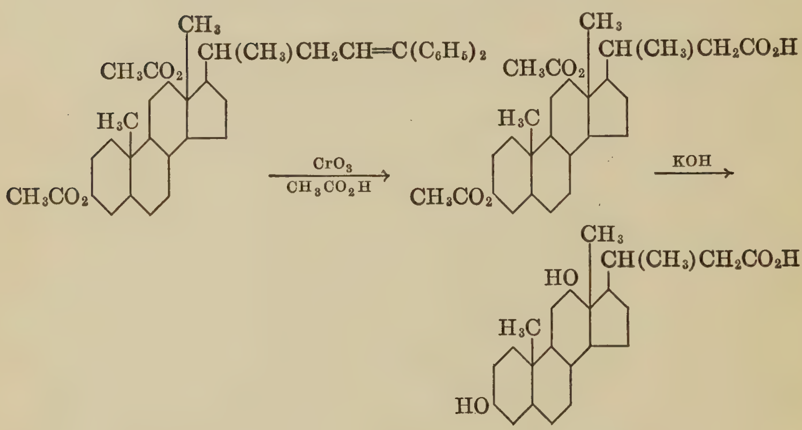
Cyclopropanecarboxylic acid has been prepared by the hydrolysis of cyclopropyl cyanide,[3] although it is unnecessary to

[2] *Org. Syntheses* Coll. Vol. **I**, 130 (1941).
[3] *Org. Syntheses*, **23**, 20 (1943).

isolate the nitrile;[4,5,6] by heating cyclopropanedicarboxylic acid;[7,8] and by the action of alkali on ethyl γ-chlorobutyrate.[9] The last two methods do not appear to be of practical importance.

## *nor*-DESOXYCHOLIC ACID

### (3,12-Dihydroxy-*nor*-cholanic acid)



Submitted by Byron Riegel, R. B. Moffett, and A. V. McIntosh.
Checked by Richard B. Turner and Louis F. Fieser.

### 1. Procedure

A solution of 59.6 g. (0.1 mole) of 3,12-diacetoxy-*bisnor*-cholanyldiphenylethylene (p. 41) in 60 ml. of chloroform is prepared by warming and poured into a 1-l. round-bottomed flask containing 300 ml. of glacial acetic acid at about 40°. The flask

[4] Henry, *Bull. sci. acad. roy. Belg.*, (3) **36**, 34 (1898) (*Chem. Zentr.*, **1899**, I, 975).

[5] Kishner, *J. Russ. phys. chem. Ges.*, **37**, 304 (*Chem. Zentr.*, **1905**, I, 1703).

[6] Bruylants and Stassen, *Bull. sci. acad. roy. Belg.*, (5) **7**, 702 (1921) (*Chem. Zentr.*, **1922**, I, 1229) [*C.A.*, **17**, 2872 (1923)].

[7] Perkin, *J. Chem. Soc.*, **47**, 815 (1885).

[8] Skraup and Binder, *Ber.*, **62**, 1132 (1929).

[9] Rambaud, *Bull. soc. chim.*, (5) **5**, 1564 (1938).

is provided with a stirrer, a thermometer dipping below the surface of the solution, and a dropping funnel, and is surrounded by a water bath through which cold water can be circulated. A solution of 37 g. of chromium trioxide in 30 ml. of water and 200 ml. of acetic acid is added from the dropping funnel at such a rate that the temperature is kept at about 50°; the mixture is stirred and cooled. This operation should require about 10 minutes. When the temperature starts to drop, the water bath is warmed and the temperature is maintained at about 50° for an additional 20 minutes. The solution is then cooled, and the excess chromic acid is destroyed by adding carefully about 30 ml. of methanol, the temperature being kept below 50° (Note 1).

The reaction mixture is concentrated by distillation under reduced pressure. At first the solvent may be distilled rapidly, but, after the mixture becomes syrupy, the distillation should be carried out below 30° until the residue is almost solid. At a pressure of 10 mm. the concentration requires about 2 hours. The residue is diluted with 500 ml. of cold water, which should be added in several portions with thorough shaking to break up all the lumps. The product is collected on a filter and washed with dilute hydrochloric acid until the filtrate comes through colorless.

The solid crystalline cake (Note 2) is dissolved in about 400 ml. of ether and extracted with 500 ml. of 2.5% potassium hydroxide solution (Note 3). The alkaline solution is immediately acidified with 200 ml. of 10% hydrochloric acid, and the crude 3,12-diacetoxy-*nor*-cholanic acid (Note 4) is collected on a filter.

The crude diacetate is hydrolyzed by dissolving it in 350 ml. of 10% aqueous potassium hydroxide and refluxing the solution for 2 hours. The alkaline solution is diluted to about 700 ml., cooled, and filtered. The filtrate is poured into 300 ml. of 10% hydrochloric acid, and the *nor*-desoxycholic acid is separated by filtration and dried. The crude product is dissolved in about 600 ml. of acetone and filtered, while hot, to remove small amounts of salt. On cooling, 25–30 g. (57–68%) of white crystals which melt at 209–211° is obtained in two crops (Note 5). This

material contains 1 molecule of acetone of crystallization. The fully purified substance softens at about 160° (loss of acetone) and melts at 213.5–214.5°.

## 2. Notes

1. Solid chromic acid and methanol will ignite spontaneously; care should be taken that the methanol does not come in contact with any of the chromic acid solution which may have dried around the edges of the dropping funnel.

2. If the cake is not nearly colorless it should be stirred with 250 ml. of 10% hydrochloric acid and the mixture extracted with 400 ml. of ether. The ether solution is then extracted with the 2.5% potassium hydroxide as described.

3. Vigorous mixing should be avoided in order to prevent the formation of an emulsion.

4. The 3,12-diacetoxy-*nor*-cholanic acid may be purified by crystallization from acetone. It melts at 207–208°.

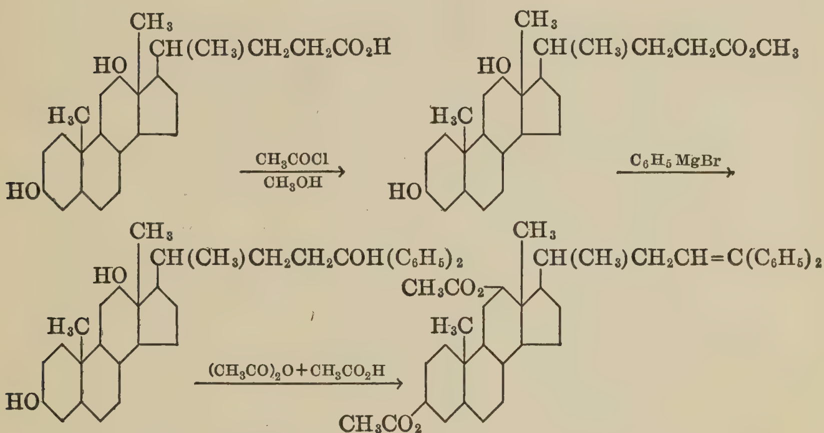
5. This procedure, coupled with the procedure described on p. 41, illustrates the Barbier-Wieland method for systematically degrading carboxylic acids. *bisnor*-Desoxycholic acid may be prepared from *nor*-desoxycholic acid by repetition of this procedure. If the chromic acid oxidation product is not sufficiently solid to filter after dilution with water, the mixture must be extracted with ether and washed with dilute hydrochloric acid before the alkaline extraction. *bisnor*-Desoxycholic acid may be crystallized from ethyl alcohol. It melts at 239–241°.

## 3. Methods of Preparation

*nor*-Desoxycholic acid has been prepared from desoxycholic acid by modification of the Barbier-Wieland degradation.[1]

[1] Hoehn and Mason, *J. Am. Chem. Soc.*, **60**, 1493 (1938); Sawlewicz, *Roczniki Chem.*, **18**, 250, 755 (1938); Kazuno and Simizu, *J. Biochem.* (*Japan*), **29**, 421 (1939); Reichstein and Arx, *Helv. Chim. Acta*, **23**, 747 (1940).

## 3,12-DIACETOXY-*bisnor*-CHOLANYLDIPHENYLETHYLENE




Submitted by BYRON RIEGEL, R. B. MOFFETT, and A. V. McINTOSH.
Checked by RICHARD B. TURNER and LOUIS F. FIESER.

### 1. Procedure

A. *Methyl desoxycholate.* To a cooled solution of 100 g. (0.255 mole) of desoxycholic acid (Note 1) in 1 l. of methanol is added carefully 50 ml. of acetyl chloride. The solution is allowed to stand overnight at room temperature (Note 2) and is then diluted with cold water until just turbid. Crystallization is induced by scratching and seeding, if necessary. When much of the ester has crystallized, the mixture is further diluted to about 2.5 l. and allowed to stand for 30 minutes until crystallization is complete. The ester is collected on a filter, washed with water, and dried. The yield is 100–103 g. (97–100%) of material which melts at 95–100° (Note 3).

B. *3,12-Diacetoxy-bisnor-cholanyldiphenylethylene.* A solution of phenylmagnesium bromide is prepared in a 5-l. three-necked flask, fitted with a dropping funnel, efficient reflux condenser, and mechanical stirrer, from 97.2 g. (4 gram atoms) of magnesium,

675 g. (450 ml., 4.3 moles) of bromobenzene, and 1250 ml. of dry ether.[1]

To the solution of the Grignard reagent is added a solution of 102 g. (0.25 mole) of methyl desoxycholate in 700 ml. of dry benzene (Note 4). The desoxycholate is washed into the flask with 500 ml. of dry benzene, and the mixture is refluxed with stirring for 3 hours. After cooling, the complex is decomposed by pouring its benzene solution into a mixture of about 4 l. of ice and 700 ml. of concentrated hydrochloric acid. After thorough shaking, the layers are separated, and the aqueous layer is extracted twice with ether. The combined ether solution is washed with dilute hydrochloric acid, water, 5% sodium hydroxide solution, and finally with water. The solvent and some biphenyl are removed by steam distillation; approximately 5 hours is required to remove the biphenyl formed during the preparation of the Grignard reagent. The lumps should be broken up from time to time, if necessary. After cooling, the residue of crude 3,12-dihydroxy-*nor*-cholanyldiphenylcarbinol is collected and dried.

The crude carbinol is acetylated and dehydrated by refluxing its solution in 1 l. of glacial acetic acid and 500 ml. of acetic anhydride for 1 hour. The solution is then concentrated to about 500 ml. by distillation. After cooling overnight, the crystalline 3,12-diacetoxy-*bisnor*-cholanyldiphenylethylene is collected on a filter and washed with acetic acid. The yield is 95–105 g. (63.5–70.0%) of material melting at 154–157° (Note 5). This product is sufficiently pure to be used for the preparation of *nor*-desoxycholic acid (p. 38); one crystallization from acetone gives white crystals which melt at 156–157.5°; fully purified material melts at 159.5–160.5°.

## 2. Notes

1. A good grade of desoxycholic acid should be used. The product from Wilson Laboratories has been found to be satisfactory.

[1] *Org. Syntheses* Coll. Vol. **I**, 226 (1941).

2. At this point the solution should be filtered if any insoluble material is present.

3. This methyl desoxycholate is pure enough for most purposes, but if desired it may be recrystallized from methanol or from a mixture of ether and petroleum ether.

4. The solution of methyl desoxycholate in dry benzene is conveniently prepared by dissolving the ester in 900 ml. of ordinary benzene and distilling the excess solvent.

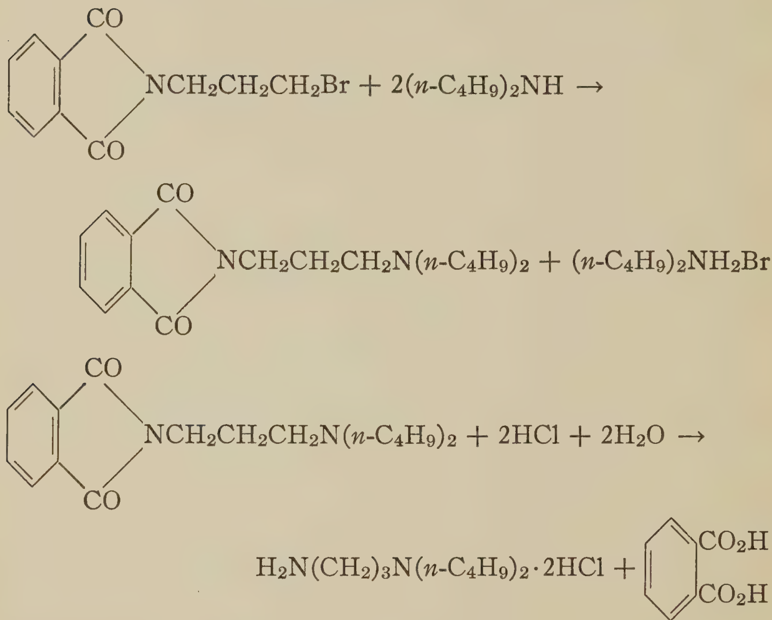
5. An additional 5–7 g. of product may be obtained by concentrating the filtrate and recrystallizing the product from acetone. If the material is to be used for the preparation of *nor*-desoxycholic acid (p. 38), it is more convenient to oxidize the filtrate directly with chromic acid and isolate the product as the acid.

### 3. Methods of Preparation

The literature on methods of preparation is the same as that given for *nor*-desoxycholic acid (p. 40).

## γ-DI-*n*-BUTYLAMINOPROPYLAMINE

### (1,3-Propanediamine, N,N-di-*n*-butyl-)




$$H_2N(CH_2)_3N(n\text{-}C_4H_9)_2 \cdot 2HCl + 2KOH \rightarrow 2KCl + 2H_2O + H_2N(CH_2)_3N(n\text{-}C_4H_9)_2$$

Submitted by LAWRENCE H. AMUNDSEN and JAMES J. SANDERSON.
Checked by R. L. SHRINER and JOHN L. RENDALL.

### 1. Procedure

In a 500-ml. distilling flask are placed 107 g. (0.40 mole) of γ-bromopropylphthalimide (Note 1) and 240 ml. of xylene. Solution is effected by heating, and 24 ml. of xylene is distilled to remove traces of moisture. After cooling, the solution is transferred to a 1-l. round-bottomed flask with a ground-glass joint and treated with 107 g. (140 ml., 0.83 mole) of di-*n*-butylamine.

The flask is fitted with a reflux condenser and heated with occasional shaking for 10 hours in an oil bath maintained at 140–150°.

The solution is allowed to cool, and the di-*n*-butylamine hydrobromide, which separates in the course of the reaction, is removed by means of a suction filter (Note 2). The filtrate is transferred to a 500-ml. distilling flask, and the xylene is removed by distillation. The crude γ-di-*n*-butylaminopropylphthalimide, a brown oil, is transferred to a 500-ml. round-bottomed flask with a ground-glass joint and treated with 20 ml. of water and 120 ml. of 12 *N* hydrochloric acid. The flask is fitted with a reflux condenser, and the solution is heated for 6 hours in an oil bath maintained at 140–150°. After the solution has cooled to room temperature, the precipitated phthalic acid is removed by filtration and washed with four 25-ml. portions of cold water. The combined filtrates are transferred to a 600-ml. beaker and heated on a steam bath to evaporate the water and hydrochloric acid.

The residue, a thick brown oil, which is crude γ-di-*n*-butylaminopropylamine dihydrochloride, is treated with a solution of 80 g. of potassium hydroxide in 80 ml. of water. A brown oil separates above the aqueous layer, which contains a considerable amount of solid potassium chloride. The whole is extracted with one 200-ml. portion and two 50-ml. portions of benzene (Note 3). The combined extracts are then placed in a 500-ml. Erlenmeyer flask over 50 g. of potassium hydroxide and allowed to dry overnight.

The dried benzene extract is placed in a 500-ml. round-bottomed flask with a ground-glass joint. The flask is fitted with a Vigreux column, and the benzene is distilled from the solution at atmospheric pressure, an oil bath maintained at 100–110° being the source of heat. The crude γ-di-*n*-butylaminopropylamine is fractionated under reduced pressure from a 250-ml. Claisen flask; heat is supplied by an oil bath maintained at 170–180°. The yield of product boiling at 108–110.5°/5–6 mm. or 98–100°/2 mm. amounts to 57–60 g. (77–80%) (Note 4).

## 2. Notes

1. The γ-bromopropylphthalimide was prepared from potassium phthalimide and trimethylene bromide in 78% yields, using the conditions and molar quantities specified for the preparation of β-bromoethylphthalimide.[1] γ-Bromopropylphthalimide can also be prepared from phthalimide, potassium carbonate, and trimethylene bromide.[2]

2. About 55–58 g. of di-*n*-butylamine hydrobromide is recovered.

3. The increase in volume of the first portion is about 75 ml. There is no noticeable increase in the volumes of the two 50-ml. portions.

4. This same procedure has been followed in the preparation of γ-diethylaminopropylamine and γ-di-*n*-propylaminopropylamine. When these substances are prepared by the method described, yields of 60% and 67% respectively are obtained.

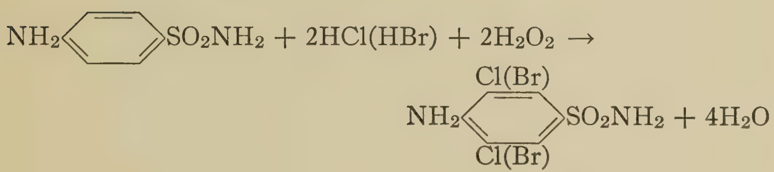
## 3. Methods of Preparation

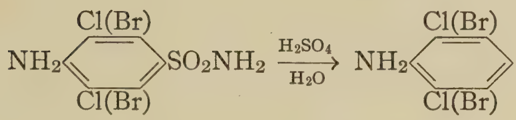
The above procedure is based on the directions of Sanderson.[3]

[1] *Org. Syntheses* Coll. Vol. **I**, 119 (1941).
[2] *Org. Syntheses* Coll. Vol. **2**, 84, note 5 (1943).
[3] Sanderson, M.S. Thesis, University of Connecticut, 1942.

# 2,6-DICHLOROANILINE AND 2,6-DIBROMOANILINE

**(Aniline, 2,6-dichloro- and 2,6-dibromo-)**





Submitted by MARGARET K. SEIKEL.
Checked by H. R. SNYDER and A. B. SPRADLING.

## 1. Procedure

A. *3,5-Dichlorosulfanilamide.* In a 2-l. round-bottomed flask, fitted with a two-holed stopper carrying a mechanical stirrer and a thermometer, are placed 50 g. (0.29 mole) of sulfanilamide and 500 ml. of water. About 50 ml. of a 500-ml. portion (approximately 6 moles) of pure concentrated hydrochloric acid is added, and the mixture is stirred until a clear solution results (Note 1). The remainder of the 500 ml. of hydrochloric acid is then added. If the internal temperature does not rise to 45°, the stirred solution should be warmed gently with a free flame until this temperature is reached. At this point 65 g. (59 ml., 0.58 mole) of 30% hydrogen peroxide (sp. gr. 1.108) is added and rapid stirring is initiated (Note 2). The heat of reaction causes a progressively faster rise in temperature. After 5 minutes the solution fills with a white precipitate which increases rapidly in amount and becomes delicately colored. When the temperature has reached 60°, about 10 minutes after adding the peroxide (Note 3), any further rise is preferably prevented by judicious cooling (Note 4). The reaction is allowed to proceed for 15

minutes more at 60°, and then an ice bath is raised about the flask while stirring is continued. When the temperature has fallen to 25–30°, the mixture is filtered at once. The yield of 3,5-dichlorosulfanilamide is 45–50 g. (65–71%), and the crude dusky pink product melts over a range of 1–2° in the region 200–205° (Note 5).

B. *2,6-Dichloroaniline.* The crude 3,5-dichlorosulfanilamide is added to 200–250 ml. (5 ml./g.) of 70% sulfuric acid (50 ml. of concentrated acid diluted with 31 ml. of water) in a 500-ml. flask, and the mixture is boiled gently for 2 hours; heat is supplied by an oil bath kept at 165–195° (Note 6). The dark mixture is then poured into 1 l. of water in a 2-l. round-bottomed flask, whereupon partial separation of a suspension of black oil occurs. The flask is attached to a condenser by a goose-neck of glass tubing; the tubing entering the flask is bent at a slight angle and cut so that its opening is at right angles to the level of the solution (Note 7). The product is steam-distilled by boiling the mixture with a free flame; the collecting vessel should be immersed in an ice bath. The solid product is separated from the distillate and dried in the air (Note 8); the white 2,6-dichloroaniline weighs 23.5–26 g. (75–80% based on 3,5-dichlorosulfanilamide or 50–55% based on sulfanilamide) and melts at 39–40°. If the product is colored it can be purified by a second steam distillation; recovery is over 90%.

C. *3,5-Dibromosulfanilamide.* The bromination of sulfanilamide is carried out in much the same way as the chlorination. The stirrer must be more efficient (Note 9); a glass stirrer with two sets of blades is satisfactory if run at high speed. Fifty grams (0.29 mole) of sulfanilamide is dissolved in a mixture of 850 ml. of water (Note 9) and 100 ml. (0.68 mole) of 40% hydrobromic acid (Note 10). The solution is heated as above, but to 70–75°, and 65 g. (59 ml., 0.58 mole) of 30% hydrogen peroxide is added (Notes 2 and 11). A precipitate settles in 2 to 3 minutes, and the solution becomes yellow. The heat of reaction causes the internal temperature to rise without further application of heat to a maximum of 85–90° after 10 minutes; by the end of the reaction time the temperature will have fallen to about

70° (Note 12). After a total reaction time of 30 minutes (Note 13), during which the mixture has become almost solid and is very difficult to stir, the material is filtered hot (Note 14). The yield of 3,5-dibromosulfanilamide is 85–90 g. (90–94%), and the crude tan product (Note 15) melts over a range of 1–2° in the region 230–237° (Note 16).

D. *2,6-Dibromoaniline.* In a 2-l. flask, equipped with a two-holed stopper carrying an exit tube to a condenser and an entrance tube for steam, 50 g. of crude 3,5-dibromosulfanilamide (Notes 17 and 18) and 250 ml. (5 ml./g.) of 70% sulfuric acid are heated in an oil bath; when the temperature of the bath reaches 175–180°, steam is passed rapidly through the mixture (Note 19). The hydrolysis is continued in this way for 2 hours; small amounts of the dibromoaniline distil (Note 20). The bath is then allowed to cool to 105–110°. At this temperature the main mass of the product is steam-distilled. The slightly colored 2,6-dibromoaniline melts at 84–86° and weighs 25–30 g. (66–79% based on 3,5-dibromosulfanilamide) (Note 21). It may be purified by recrystallization from 70% alcohol (7 ml./g.); after recrystallization the product is obtained as long colorless needles which melt at 87–88°. The recovery is 85–90%.

## 2. Notes

1. Solution of sulfanilamide is more readily obtained in this way than by treating the amide at once with 6 *N* acid for, in the latter case, the salt precipitates at first and redissolves only slowly. If acid stronger than 6 *N* is used, a larger volume is required to dissolve the sulfanilamide hydrochloride, and the product is partly held in solution as dichlorosulfanilamide hydrochloride unless the solution is diluted. If 4 *N* acid is used, the reaction is much slower without any worthwhile decrease in the color of the product.

2. Equivalent quantities of sulfanilamide and hydrogen peroxide are used in order to minimize the cost since no better yields are obtained with either in excess. If sulfanilamide is in

excess, the product is tinged more orange-tan than pink and never becomes red from subsequent oxidation. If hydrogen peroxide is in excess, the reaction is faster but rapid oxidation giving dark-colored materials occurs toward the end.

3. When smaller amounts of reactants are employed, it is necessary to apply heat to reach and maintain a temperature of 60°.

4. Without cooling, the temperature rises above 70° and the precipitate becomes deep rose from oxidation by-products. This color, however, does not seem to affect the yield or purity of the dichloroaniline to any great extent.

5. The color of the product varies; higher temperatures, larger excesses of peroxide, longer reaction times, higher acidity, and higher concentrations of the reactants lead to the formation of more deeply colored materials. The color may be removed by several recrystallizations from glacial acetic acid with decolorizing carbon. As a preparative method for dichlorosulfanilamide, when a pure product is desired, the following procedure is recommended. For each 10 g. (0.058 mole) of sulfanilamide, 200 ml. of water, 200 ml. of concentrated hydrochloric acid, and 24 ml. (0.23 mole or 2 equivalents) of 30% hydrogen peroxide are used and the reaction is run at 25° for not more than 2 hours. A practically white product is obtained in 45–60% yield. It may be recrystallized from a very large volume of water, from 95% alcohol, or from glacial acetic acid; the recrystallized product melts at 205–205.5°.

6. Desulfonamidation is brought about faster by 75% sulfuric acid, but the yield is lower. The reaction is inconveniently slow with 65% sulfuric acid.

7. This bend prevents the mechanical carry-over of dark materials from the spray rising from the boiling dark solution. A distilling flask is not employed because dark oil creeps out the side arm.

8. It is difficult to measure the yield accurately; the material must be air-dried on account of its low melting point; the substance volatilizes to a significant extent on standing.

9. The larger amount of product obtained requires a more

dilute initial solution coupled with violent stirring to maintain sufficient agitation.

10. Speedier reactions can be run at lower temperatures, producing lighter-colored crude materials if the amount of hydrobromic acid is doubled (30 minutes at 45°) or quadrupled (20 minutes at 25°); the use of the minimum quantity recommended above (approximately 1.15 times the required amount) produces as high yields of as high-melting materials with an attendant reduction in cost.

The 100 ml. of 40% hydrobromic acid can be replaced by 75 ml. of 48% hydrobromic acid.

11. The use of excess peroxide in the bromination also causes the formation of tribromoaniline.[1,2,3,4] If only 0.29 mole of hydrogen peroxide is used, the monobromo derivative is obtained.

12. When small runs are made, it is necessary to use a bath to attain and maintain an internal temperature of 80–85° during the reaction time of 30 minutes.

13. The reaction is considered complete when a sudden increase in or appearance of the brownish yellow color of free bromine is noted. This may or may not be evident under the above conditions, for the solution is deeply colored because of the high temperature and a very slight excess of hydrobromic acid is used; it is clearly evident whenever the excess is greater or the temperature lower.

14. Hot filtration removes traces of the monobromo compound, which is soluble in water and acids.

15. When the reaction is run at lower temperature with excess hydrobromic acid, the crude product is lighter colored. However, it melts no higher and is purified with no greater ease and with only slightly better recovery.

16. The purification of the crude material is effected by recrystallization from glacial acetic acid or, preferably, 95% alcohol (25 ml./g.), using decolorizing carbon; colorless needles,

[1] Heinichen, *Ann.*, **253**, 274 (1889).
[2] Heinichen, *Ann.*, **253**, 269 (1889).
[3] Orton and Pearson, *J. Chem. Soc.*, **93**, 735 (1908).
[4] Sudborough and Lakhumalani, *J. Chem. Soc.*, **111**, 45 (1917).

which melt at 239–240°, are obtained after two recrystallizations.

17. The crude material to be used for desulfonamidation should be tested for absence of *sym.*-tribromoaniline by ascertaining its solubility in 1 *N* alkali. A clear, though colored, solution should result. If the solution is cloudy, purification of the impure material by dissolving it in alkali, filtering the solution, and reprecipitating the amide is essential.

18. Fifty-gram lots seemed to be the maximum size if consistently high-melting pure material is to be obtained under the conditions employed. If a very pure product is desired, less starting material should be used.

19. The use of a current of steam in the desulfonamidation of the dibromo compound as recommended by earlier investigators [1,3,5] was found to be absolutely necessary in this instance. Without the steam, considerable amounts of *sym.*-tribromoaniline are formed; [6] superheated steam is not necessary. The purity of the crude product varies directly with the ratio of the amount of steam to the size of the reaction mixture; the current of steam should be very rapid or the amount of material in a single operation should be small.

20. One and a half liters of distillate was collected in the time given.

21. If the crude product melts lower, it contains too much tribromoaniline to permit satisfactory purification. Recrystallization effects no separation; repeated fractional steam distillation is very slowly effective.

## 3. Methods of Preparation

2,6-Dichloroaniline was prepared by Beilstein [7] and by Körner [8] by reduction of 2,6-dichloronitrobenzene. A better method, more recently reported,[9] involves the chlorination of

[5] Montagne and Moll Van Charante, *Rec. trav. chim.*, **31**, 334 (1912).

[6] Limpricht, *Ber.*, **10**, 1541 (1877).

[7] Beilstein and Kurbatow, *Ann.*, **196**, 219, 228 (1879).

[8] Körner and Contardi, *Atti accad. Lincei*, (5) **18**, I, 100 [*C.A.*, **4**, 1619 (1910)].

[9] Dyson, George, and Hunter, *J. Chem. Soc.*, **1926**, 3043.

sulfanilic acid in 1% solution with free chlorine, subsequent evaporation of the solution, and desulfonation as above. The present method (reported earlier in slightly different form and for small amounts [10]), although requiring more expensive raw materials, is more convenient and gives higher yields.

2,6-Dibromoaniline has been prepared many times [1,3,5,6,11] by bromination of sulfanilic acid and desulfonation of the product or its salts. Fuchs [12] brominated sulfanilamide with free bromine and desulfonamidated it in the usual manner. Reduction of the corresponding nitro compound [13] and other methods [14] also have been employed.

## DIPHENYLDIAZOMETHANE

**(Methane, diazodiphenyl-,)**

$$(C_6H_5)_2CO + H_2NNH_2 \rightarrow (C_6H_5)_2C{=}NNH_2 + H_2O$$
$$(C_6H_5)_2C{=}NNH_2 + HgO \rightarrow (C_6H_5)_2CN_2 + H_2O + Hg$$

Submitted by Lee Irvin Smith and Kenneth L. Howard.
Checked by H. R. Snyder, R. L. Rowland, and H. J. Sampson, Jr.

### 1. Procedure

A. *Anhydrous hydrazine* (Note 1). A 250-ml. distilling flask is set in an oil bath and connected to a condenser by means of a cork covered with tin foil (Note 2); a 250-ml. suction flask is used as the receiver. This flask carries a calcium chloride guard tube and is connected to a condenser through a cork covered with tin foil. In the distillation flask are placed 60 g. of 85% aqueous hydrazine hydrate (Note 3) and 60 g. of sodium hydroxide pellets (Note 4). The temperature of the oil bath is raised

[10] Seikel, *J. Am. Chem. Soc.*, **62**, 1214 (1940).
[11] Willgerodt, *J. prakt. Chem.*, (2) **71**, 562 (1905).
[12] Fuchs, *Monatsh.*, **36**, 124 (1915).
[13] Claus and Weil, *Ann.*, **269**, 220 (1892).
[14] Buning,, *Rec. trav. chim.*, **40**, 345, 347 (1921).

to 113° and is maintained within 2° of this temperature for 2 hours. The temperature of the bath is then gradually raised to 150°; during this process the liquid hydrazine distils into the receiver. The anhydrous hydrazine weighs 30–30.5 g. (94–95.5%). The product is pure enough for use in the next step.

B. *Benzophenone hydrazone.* A hydrogenation bomb is charged with 25.2 g. (0.138 mole) of benzophenone, 7.46 g. (0.23 mole) of anhydrous hydrazine, and 14 ml. of absolute alcohol. The bomb is closed with a safety head instead of the usual pressure gauge assembly and is then heated for 4 hours at 150°. After the bomb has cooled, it is opened and the benzophenone hydrazone is removed from the mixture. It weighs 26.4 g. and melts at 94–99°. After recrystallization from 75 ml. of 95% alcohol, the hydrazone forms long white needles which melt at 97–98° and weigh 21.5–22.0 g. (80–82%).

C. *Diphenyldiazomethane.* In a pressure bottle are placed 19.6 g. (0.1 mole) of benzophenone hydrazone, 22 g. (0.1 mole) of yellow oxide of mercury, and 100 ml. of petroleum ether (b.p. 30–60°). The bottle is closed, wrapped in a wet towel, and shaken mechanically at room temperature for 6 hours. The mixture is then filtered to remove mercury and any benzophenone azine (Note 5), and the filtrate is evaporated to dryness under reduced pressure at room temperature. The crystalline residue of diphenyldiazomethane melts when its temperature reaches that of the room (Note 6), but it is difficult to purify and this product is pure enough for all practical purposes. The material weighs 17.3–18.6 g. (89–96%). The product should be used immediately (Note 7).

## 2. Notes

1. The submitters found this method for the preparation [1] of anhydrous hydrazine to be superior to that given elsewhere.[2]

2. In any apparatus for handling anhydrous hydrazine, all connections must be made through tightly fitting corks which are covered with tin foil.

[1] Raschig, *Ber.*, **43**, 1927 (1910).
[2] *Org. Syntheses*, **21**, 70 (1941).

3. Commercial 85% hydrazine hydrate, obtained from the Eastman Kodak Company, was used.

4. If pellets are not available, stick sodium hydroxide is crushed in a mortar to pea size and is quickly transferred to the flask.

5. This ketazine is insoluble in petroleum ether.

6. The reported melting point of diphenyldiazomethane is 29–30°,[3] but this melting point is shown only after the substance has been recrystallized from petroleum ether.

7. On standing, diphenyldiazomethane decomposes to yield benzophenone azine. In one of the checkers' runs the product was stored at room temperature; after 2 days, crystals of the azine were visible. The product at this stage was assayed by treatment with benzoic acid; addition of 6.8 g. of the diazo compound in a thin stream to a solution of 17 g. of benzoic acid in 90 ml. of ether, and, after 30 minutes, extraction of the excess benzoic acid with dilute sodium hydroxide followed by distillation of the ether, gave 7.4 g. (75%) of crude benzohydryl benzoate melting at 83–85°. In the same procedure the freshly prepared diazo compound gave a quantitative yield of the crude ester.

### 3. Methods of Preparation

Diphenyldiazomethane has been prepared only by oxidation of benzophenone hydrazone.[3] The procedure given above is that of Staudinger, Anthes, and Pfenninger, with minor changes. The method of preparation of benzophenone hydrazone given above is a modification of the procedure of Curtius and Rauterberg.[4]

[3] Staudinger, Anthes, and Pfenninger, *Ber.*, **49**, 1932 (1916).

[4] Curtius and Rauterberg, *J. prakt. Chem.*, (2) **44**, 194 (1891).

## ETHYL DIAZOACETATE

**(Acetic acid, diazo-, ethyl ester)**

$$CH_2(NH_3Cl)CO_2C_2H_5 + NaNO_2 \rightarrow N_2CHCO_2C_2H_5 + NaCl + 2H_2O$$

Submitted by Ennis B. Womack and A. B. Nelson.
Checked by R. L. Shriner and C. H. Tilford.

### 1. Procedure

A 1-l. three-necked round-bottomed flask is fitted with a 50-ml. separatory funnel and a mechanical stirrer sealed with a well-lubricated rubber collar. A stopper in the third neck of the flask carries a glass tube that reaches to the bottom of the flask, enters the top of a 1-l. separatory funnel, and extends down to the stopcock.

A solution of 140 g. (1 mole) of glycine ethyl ester hydrochloride [1] and 3 g. of sodium acetate in 150 ml. of water is added to the flask and cooled to 2° by means of an ice-salt bath. A cold solution of 80 g. (1.15 moles) of sodium nitrite in 100 ml. of water is added, and the mixture is stirred until the temperature has fallen to 0°. The temperature is maintained below 2°, and stirring is continued throughout all the following operations. To the cold mixture are added 80 ml. of cold, alcohol-free ethyl ether (Note 1) and 3 ml. of cold 10% sulfuric acid. After 5 minutes, the reaction mixture is blown over into the 1-l. separatory funnel by application of air pressure. The lower aqueous layer is *quickly* sucked back into the reaction flask. The ether layer is removed and immediately washed with 50 ml. of cold 10% sodium carbonate solution. This ether solution should be neutral to moist litmus paper; if not, the washing with sodium carbonate is repeated. The ether solution is finally dried over 10 g. of anhydrous sodium sulfate.

[1] *Org. Syntheses* Coll. Vol. **2**, 310 (1943).

A second portion of 80 ml. of alcohol-free ether is then added to the reaction mixture with stirring, followed by 15 ml. of cold 10% sulfuric acid over a period of 5 minutes. After 3 minutes' contact (Note 2), the ether layer is removed as before, washed immediately with 50 ml. of fresh 10% sodium carbonate solution, and dried over 10 g. of sodium sulfate. This procedure is repeated (about 6 or 7 times) until the ether layer is no longer yellow.

The combined ether solutions are then subjected to distillation at 20° or below under the vacuum obtainable from a water pump until all the ether is removed. Prolonged distillation results in decomposition of the diazo ester and in a decreased yield. The yellow residual oil is practically pure ethyl diazoacetate and is satisfactory for most synthetic purposes (Note 3). The yield is about 98 g. (85%) (Notes 4 and 5).

## 2. Notes

1. The alcohol is removed from 600 ml. of commercial ethyl ether by thorough washing with 75 ml. of a saturated calcium chloride solution.

2. The ether layer should be removed as rapidly as possible from the aqueous layer, because ethyl diazoacetate is rapidly decomposed by acid.

3. Ethyl diazoacetate may be purified, but with considerable loss, by steam distillation under reduced pressure.[2]

4. The submitters have carried out preparations using twice the amounts stated.

5. The product should be placed in dark brown bottles and kept in a cool place. It should be used as soon as possible. *Distillation, even under reduced pressure, is dangerous, for the substance is explosive.*

[2] Gattermann, *Laboratory Methods of Organic Chemistry*, p. 268, The Macmillan Company, New York, 1934.

### 3. Method of Preparation

Ethyl diazoacetate has been prepared by the action of sodium nitrite on glycine ethyl ester hydrochloride.[3]

## ETHYL HYDRAZINECARBOXYLATE

## (Carbazic acid, ethyl ester)

## AND DIAMINOBIURET

$$2N(CO_2C_2H_5)_3 + 5NH_2NH_2 + H_2O \rightarrow 3NH_2NHCO_2C_2H_5 + NH(CONHNH_2)_2 + CO_2 + 3C_2H_5OH + NH_3$$

Submitted by C. F. H. Allen and Alan Bell.
Checked by Nathan L. Drake and Carl Blumenstein.

### 1. Procedure

In a 3-l. round-bottomed flask equipped with a reflux condenser are placed 582 g. (2.5 moles) of N-tricarboxylic ester (p. 60) and 800 g. (6.7 moles) of 42% hydrazine hydrate (Note 1). The flask is shaken by hand to mix the two layers. After a short time, reaction begins with considerable evolution of heat, and all the N-tricarboxylic ester goes into solution (Note 2). After the reaction subsides, the solution is heated for 1 hour on a steam bath and then evaporated under reduced pressure until the mixture becomes a thick slurry of diaminobiuret crystals (Note 3). The mixture is cooled, 2 l. of 95% ethanol is added, and the diaminobiuret which has crystallized is filtered, washed with 250 ml. of ethanol, and dried. The substance melts at 205° with decomposition. The yield is 115–125 g. (69–75%).

The filtrate is now evaporated at atmospheric pressure to remove the alcohol, and the residual oil is distilled using a Vigreux column. Ethyl hydrazinecarboxylate boils at 92–95°/

[3] Curtius, *J. prakt. Chem.*, (2) **38**, 396 (1888); Silberrad, *J. Chem. Soc.*, **81**, 600 (1902).

13 mm. The yield is 350–370 g. (90–95%). After distillation in vacuum, the ester may crystallize; the crystals melt at 51–52°.

## 2. Notes

1. This reaction can be carried out successfully with these amounts, but, if larger quantities of starting materials were to be used, it would be advisable to dilute the ester with alcohol and run in the hydrazine slowly. Several hours of refluxing on a steam bath would serve to complete the reaction. In smaller runs no difficulty is encountered.

2. It is advisable to keep an ice bath at hand in case the reaction becomes too violent and it is necessary to cool the mixture rapidly.

3. If insufficient water is removed by evaporation, too much diaminobiuret will remain in solution and will interfere during the distillation of the ethyl hydrazinecarboxylate.

## 3. Methods of Preparation

Diaminobiuret has been prepared only from N-tricarboxylic ester and hydrazine hydrate.[1] Ethyl hydrazinecarboxylate has been prepared by reduction of nitrourethan electrolytically [2] or with zinc dust and acetic acid,[3] and by the action of hydrazine hydrate on diethyl carbonate,[4,5] ethyl chlorocarbonate,[6] and N-tricarboxylic ester.[1]

[1] Diels, *Ber.*, **36**, 736 (1903).
[2] Backer, *Rec. trav. chim.*, **31**, 20 (1912).
[3] Thiele and Lachmann, *Ann.*, **288**, 293 (1895).
[4] Diels, *Ber.*, **47**, 2186 (1914).
[5] Merck, Ger. pat. 285,800 [*Frdl.*, **12**, 94 (1914–1916)].
[6] Stollé and Benrath, *J. prakt. Chem.*, (2) **70**, 276 (1904).

# ETHYL N-TRICARBOXYLATE

## (N-Tricarboxylic ester)

$$NH_2CO_2C_2H_5 + 2ClCO_2C_2H_5 + 2Na \rightarrow N(CO_2C_2H_5)_3 + 2NaCl + H_2$$

Submitted by C. F. H. Allen and Alan Bell.
Checked by Nathan L. Drake and Carl Blumenstein.

### 1. Procedure

In a 12-l. round-bottomed flask equipped with stirrer, dropping funnel, and efficient reflux condenser are placed 450 g. (5 moles) of urethan (m.p. 46–48°), 7.5 l. of dry ether, and 218 g. of sodium wire (Notes 1 and 2). The mixture is warmed, and evolution of hydrogen accompanied by formation of sodium compound soon begins; after 2 to 3 hours the greater part of the metal will have been replaced by a gelatinous white precipitate. The stirrer is now started and the mixture warmed under reflux for an additional 2 hours. The flask is then cooled externally with running water, and 1050 g. (9.6 moles) of ethyl chlorocarbonate is added slowly over a period of 2 hours. The gelatinous precipitate becomes powdery, and the remainder of the sodium dissolves. After all the ester has been added, the mixture is stirred overnight at room temperature and then filtered (Note 3). The white residue is washed with 1 l. of ether, and the ether is removed from the combined solutions by evaporation on a steam bath (Note 4). The residual oil is distilled; after a fore-run containing some urethan, the product distils at 143–147°/12 mm. The yield is 575–640 g. (51–57%). On redistillation, all the product boils at 146–147°/12 mm.

### 2. Notes

1. Since water is usually present, it is advisable to distil the urethan before use, discarding the first 10%.

2. Sodium wire is not essential. The reaction will proceed just as well with sodium cut into pieces the size of a small pea. It is important that the sodium be cut into *small* pieces; otherwise a protective coating forms on the surface of the metal, preventing further reaction.

3. The sodium chloride is very finely divided and quickly clogs the pores of the filter paper. The mixture should be allowed to stand for a time before filtration to allow the salt to settle; the clear supernatant liquor can then be filtered rapidly.

4. Care should be taken in disposing of this residue; it invariably contains some unreacted sodium.

### 3. Methods of Preparation

Ethyl N-tricarboxylate has been prepared from urethan by reaction with sodium and chlorocarbonic ester[1] as well as from the potassium salt of ethyl imidodicarboxylate.[2]

## GLYOXAL BISULFITE

$$(CH_3CHO)_3 + 3H_2SeO_3 \rightarrow 3OHCCHO + 3Se + 6H_2O$$

$$OHCCHO + 2NaHSO_3 + H_2O \rightarrow OHCCHO \cdot 2NaHSO_3 \cdot H_2O$$

Submitted by ANTHONY R. RONZIO and T. D. WAUGH.
Checked by C. F. H. ALLEN and J. VAN ALLAN.

### 1. Procedure

In a 2-l. round-bottomed flask, attached to an efficient reflux condenser (Note 1) and set in a hot water bath, are placed 222 g. (1.72 moles) of selenious acid (Note 2), 270 ml. of paraldehyde (Note 3), 540 ml. of dioxane, and 40 ml. of 50% acetic acid (Note 4), and the mixture is refluxed for 6 hours (Note 5). The solution is then decanted from the inorganic material (Note 6),

[1] Diels, *Ber.*, **36**, 740 (1903).
[2] Diels, *Ber.*, **36**, 742 (1903).

which is washed with two 150-ml. portions of water. The combined solutions are steam-distilled through a still head [1] until the paraldehyde and dioxane have been removed; this requires about 3.5 hours (Note 7). The mixture is decanted from a little selenium (Note 6), and to the solution, without filtration, is added a slight excess of 25% lead acetate solution (Notes 8 and 9). The lead selenite is removed by filtration, and the filtrate is saturated with hydrogen sulfide in a hood (Note 8). Then 20 g. of Norite is added; the whole is warmed to 40° in a hood and filtered with suction. The water-clear solution is concentrated on a hot water bath under reduced pressure to about 150 ml. in the usual apparatus (Note 10).

This concentrate is added to a previously prepared and filtered solution of sodium bisulfite in 40% alcohol (Note 11) contained in a 4-l. beaker provided with a mechanical stirrer (Note 12). The mixture is stirred for 3 hours, and the addition product then is filtered with suction on an 18-cm. Büchner funnel and washed, first with two 150-ml. portions of alcohol and then with 150 ml. of ether. The yield of air-dried product is 350–360 g. (72–74%, based on the selenious acid used) (Note 13).

## 2. Notes

1. The loss of large quantities of acetaldehyde is avoided by use of a spiral condenser, with sufficient heating so that a vapor lock is formed—the entrapped liquid should fill about two-thirds of the spiral. In cold weather, the tap water is usually cold enough so that any efficient long condenser, or two in series, is sufficient.

2. The selenious acid does not need to be freshly prepared. A larger amount does not increase the yield. The submitters specified selenium dioxide as the oxidizing agent, but the checkers prepared their material by evaporating an aqueous solution to dryness on the water bath. They, therefore, have considered the oxidizing agent to be selenious acid and have calculated the

[1] *Org. Syntheses*, **22**, 11 (1942).

yield on this basis. If this product is in reality selenium dioxide, then the yield is 62–64%, and 222 g. is 2.0 moles.

3. This amount of paraldehyde represents a considerable excess over the theoretical but was found to be most satisfactory.

4. Acetic acid appears to function both as an accelerator for the oxidation and an inhibitor of the rearrangement to glycolic acid.

5. This is regulated by the temperature of the water bath, 65–80° being the required range.

6. This material, impure selenium, may be reoxidized,[2] and then it is suitable for a subsequent preparation. About 130 g. is recovered at this point, and 8–10 g. after the concentration.

7. Alternatively, direct distillation may be employed; this requires only 2.5 hours but demands more attention. The volume is reduced to 200–300 ml., and then 800 ml. of water is added.

8. A test sample is filtered, and the clear filtrate is treated with more of the reagent to determine the end point.

9. Lead acetate is more satisfactory than sulfur dioxide for the removal of selenious acid, provided that the solution is kept cool and a large excess is avoided.

10. This volume of solution is most easily handled. Should glyoxal itself be desired, the solution may be evaporated to dryness in a desiccator. The product thus obtained is identical with that sold as "polyglyoxal."

11. The solution is prepared by dissolving 312 g. of technical sodium bisulfite in 2.1 l. of warm (about 40°) water, and adding 1.4 l. of 95% ethyl alcohol.

12. Alternatively, this may be done in a flask, which is shaken by hand frequently to prevent formation of a solid cake. The use of a stirrer results in a granular product. The mother liquor retains about 7 g. of glyoxal bisulfite per liter.

13. This product is pure enough for most purposes. It can be recrystallized by dissolving it in water and adding enough alcohol to make a 40% solution. The recovery is 90–92%.

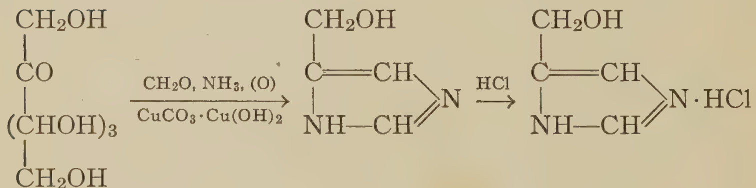
[2] *Org. Syntheses* Coll. Vol. **2**, 510, Note 2 (1943).

### 3. Methods of Preparation

Glyoxal has been obtained by several methods, only a few of which are of preparative value. The most feasible are the oxidation of acetaldehyde by nitric [3,4,5] or selenious [6] acid; the hydrolysis of dichlorodioxane; [7] and the hydrolysis of the product resulting from the action of fuming sulfuric acid upon tetrahaloethanes.[8]

## 4(5)-HYDROXYMETHYLIMIDAZOLE HYDROCHLORIDE

### (4-Imidazolemethanol, hydrochloride)




Submitted by John R. Totter and William J. Darby.
Checked by H. R. Snyder and R. L. Rowland.

### 1. Procedure

A. *Hydroxymethylimidazole picrate.* To 222 g. (1 mole) of basic cupric carbonate (Note 1) in a 5-l. flask are added 1.5 l. of distilled water and 720 g. (800 ml., 12 moles) of 28% ammonia. The bulk of the copper carbonate is brought into solution by swirling; 112 g. (100 ml., 1.3–1.4 moles) of 37–40% formaldehyde and 90 g. (0.475 mole) of commercial 95% fructose are added. The solution is well mixed and placed on a steam bath

[3] Lubawin, *Ber.*, 8, 768 (1875).
[4] Wyss, *Ber.*, **10**, 1366 (1877).
[5] Behrend and Kölln, *Ann.*, **416**, 230 (1918).
[6] Riley, Morley, and Friend, *J. Chem. Soc.*, **1932**, 1881.
[7] Butler and Cretcher, *J. Am. Chem. Soc.*, **54**, 2988 (1932).
[8] Ott Ger. pat. 362,743 [*C.A.*, **18**, 991 (1924)].

under a hood. After 30 minutes of heating with occasional shaking, a moderate current of air is bubbled through the solution (500–600 ml. per minute) (Note 2), with continued heating, for 2 hours longer (Note 3).

The mixture is then chilled in an ice bath for at least 3 hours, and the olive-brown precipitate of the sparingly soluble copper complex of imidazole derivatives is filtered. The product is washed with about 500 ml. of cold water, suspended while moist (Note 4) in 1 l. of water, and rendered just acid to litmus by the addition of concentrated hydrochloric acid (about 40 ml.). Hydrogen sulfide is then passed into the suspension, with frequent shaking, until precipitation of the copper is complete (2–3 hours). The precipitate is filtered and extracted with 500 ml. of hot water in two or three portions. The clear, light brown to reddish brown filtrate and washings are boiled for 15 minutes, and then 60 g. (0.26 mole) of picric acid is added with stirring; heating is continued until solution is complete.

The greenish yellow plates, which separate as the solution is cooled to room temperature, are filtered, washed 3 times with 150- to 200-ml. portions of water, and air-dried. The filtrate and first washings are combined and heated, 10 g. of picric acid is added, and the mixture is cooled and filtered. This process is repeated, using 10-g. portions of picric acid, until the air-dried picrate fraction so obtained melts below 195° (Note 5).

All fractions melting above 200° (Note 5) are combined and recrystallized from water by adding 700 ml. of water for each 30 g. of crystals, heating the mixture in a covered beaker until solution occurs, treating with charcoal, and filtering through a warm funnel. The crystals deposit upon the slightest cooling. After cooling, the yellow needles (occasionally plates) are filtered, washed, and air-dried; their melting point is 204° or higher, with decomposition (Note 5). The fractions melting at 195–200° (Note 5) are recrystallized in like manner until the melting point is raised to 203°. The yield of crude picrate is 95–100 g. (61–64%); of recrystallized picrate, 84–94 g. (54–60%) (Note 6). The melting point varies slightly with the rate of heating between 203.5° and 206° with decomposition (Note 5).

B. *Hydroxymethylimidazole hydrochloride.* One hundred and twenty grams (100 ml., 1.2 moles) of 37% hydrochloric acid, 250 ml. of water, and 500 ml. of benzene are placed in a 2-l. round-bottomed flask, which is then immersed in a water bath maintained at 80°. One hundred grams of the pure picrate (0.306 mole) is added to this mixture, and the flask is shaken thoroughly until the picrate dissolves. The benzene layer is decanted. The aqueous layer is then extracted 5 times with 330-ml. portions of benzene, treated with about 3 g. of Norite, and filtered through a wet filter paper. The clear, pale yellow filtrate is evaporated to dryness at 60–70° under reduced pressure. The resulting pale yellow to slightly brown crystals are taken up in the minimum quantity (30–35 ml.) of hot absolute ethyl alcohol. Colorless needles deposit on cooling. Three to four volumes of ethyl ether are added, and the mixture is kept in the refrigerator overnight. The almost colorless needles are filtered and, after being washed with a small amount of ether, are dried in a vacuum desiccator. The yield amounts to 37–39 g. (90–95%) of a product which melts at 107–109° after sintering a few degrees lower (Note 6).

## 2. Notes

1. Equally good results are obtained with technical or pure grades of basic copper carbonate, $CuCO_3 \cdot Cu(OH)_2$. Satisfactory results are obtained also when the reagent is prepared by adding an equivalent amount of a solution of sodium carbonate to a solution of copper sulfate and washing the resulting precipitate until it is nearly free of sulfate ion. When the reagent is prepared in this way, 4 moles of copper sulfate are used for each mole of fructose, and the wet basic cupric carbonate is used without drying or weighing.

2. If the aeration is omitted, the yield is about 10% lower.

3. No attempt is made to recover ammonia which escapes during the aeration.

4. The copper precipitate can be dried unchanged but is then difficult to decompose with hydrogen sulfide.

5. One to three such additions usually are necessary. The melting points given are those of the submitters and were observed by immersing the capillary melting-point tubes containing the samples in a bath preheated to a temperature 20° to 50° below the expected melting point and heating rather rapidly. The checkers determined the melting points in the ordinary manner, starting with the bath at room temperature, and observed melting points about 5° lower than those of the submitters. In one of the checkers' preparations the main fraction of crude picrate weighed 86 g. and melted at 193–194°; the second fraction weighed 12 g. and melted at 191–193°; the third fraction, which melted at 186–188°, was rejected. One recrystallization raised the melting point of the first fraction to 199° (75 g. recovered) and that of the second fraction to 197° (9.5 g. recovered). The once-recrystallized products were combined and employed in the preparation of the hydrochloride, which was obtained in the yield described and with a melting point of 107–108°.

6. Equally good yields are obtainable with double the quantities indicated.

## 3. Methods of Preparation

4(5)-Hydroxymethylimidazole has been synthesized in a long series of steps from citric acid.[1] Weidenhagen and Herrmann prepared it from dihydroxyacetone.[2] The reaction which provides the basis of the procedure here described [3] was discovered by Parrod [4] and developed by Weidenhagen, Herrmann, and Wegner.[5] The method developed by these last-named investigators, however, provides considerably smaller yields than that described above.

[1] Pyman, *J. Chem. Soc.*, **99**, 668 (1911); Koessler and Hanke, *J. Am. Chem. Soc.* **40**, 1716 (1918).

[2] Weidenhagen and Herrmann, *Ber.*, **68**, 1953 (1935).

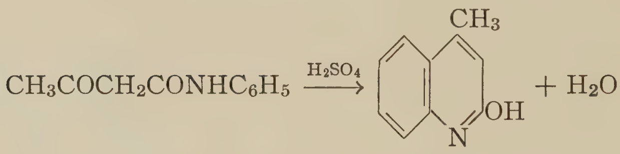
[3] Darby, Lewis, and Totter, *J. Am. Chem. Soc.*, **64**, 463 (1942).

[4] Parrod, *Bull. soc. chim.*, (4) **51**, 1424 (1932).

[5] Weidenhagen, Herrmann, and Wegner, *Ber.*, **70**, 570 (1937).

## 4-METHYLCARBOSTYRIL

**(Carbostyril, 4-methyl-)**




Submitted by W. M. Lauer and C. E. Kaslow.
Checked by C. F. H. Allen and H. W. J. Cressman.

### 1. Procedure

One hundred seventy-seven grams (1 mole) of acetoacetanilide [1] is added in small portions by means of a spatula to 185 ml. of concentrated sulfuric acid which has been heated previously to 75° (Note 1) in a 1-l. three-necked flask provided with a mechanical stirrer and a thermometer which extends into the liquid. The temperature of the mixture is maintained at 70–75° by intermittent cooling until nearly all the acetoacetanilide has been added. The last 10–15 g. is added without cooling, and the temperature rises to 95°; the addition requires 20–30 minutes. The heat of reaction maintains the temperature at 95° for about 15 minutes; the reaction mixture is then kept an additional 15 minutes at 95° by external heating. After the solution has cooled to 65°, it is poured into 5 l. of water with vigorous stirring.

After cooling, the product is filtered by suction, washed with four 500-ml. portions of water and two 250-ml. portions of methanol, and air-dried. The yield of 4-methylcarbostyril is 138–144 g. (86–91%). This material, which melts at 219–221°, is suitable for preparing 2-chlorolepidine (p. 28). It may be purified further by recrystallization from 95% ethanol. For recrystallization 39 g. is dissolved in 650 ml. of solvent; the recovery is 33–33.5 g., and the melting point of the product is 222–224°.

[1] *Org. Syntheses*, **21**, 4 (1941).

## 2. Note

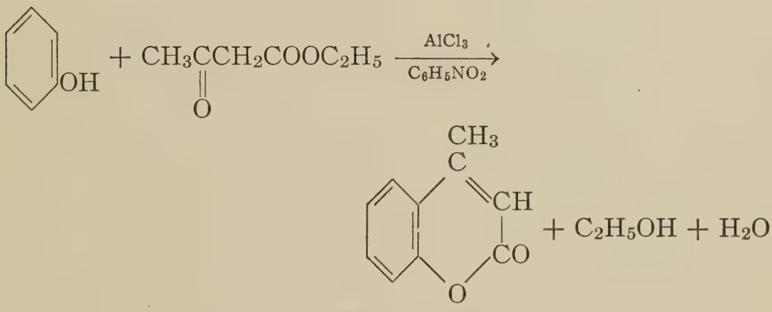
1. The reaction flask must be so situated that it can be cooled rapidly. The submitter reports that the yield was reduced to 72% in one run in which the temperature reached 120°.

## 3. Methods of Preparation

The only useful method for preparing 4-methylcarbostyril is that of Knorr,[2] recently described by Mikhaĭlov.[3]

# 4-METHYLCOUMARIN

## (Coumarin, 4-methyl-)




Submitted by Eugene H. Woodruff.
Checked by Nathan L. Drake and Carl Blumenstein.

## 1. Procedure

In a 5-l. three-necked, round-bottomed flask, fitted with a sealed stirrer, dropping funnel, and air condenser, the open end of which is connected to a gas-absorption trap, are placed 188 g. (2 moles) of phenol and 268 g. (2 moles) of ethyl acetoacetate in

[2] Knorr, *Ann.*, **236**, 83 (1886).
[3] Mikhaĭlov, *J. Gen. Chem.* (*U.S.S.R.*), **6**, 511 (1936) [*C.A.*, **30**, 6372 (1936)

300 ml. of dry nitrobenzene (Notes 1 and 2). The mixture is heated to 100° by means of an oil bath, stirring is started, and 532 g. (4 moles) of anhydrous aluminum chloride dissolved in 2.1 l. of dry nitrobenzene is added over a period of 30 to 45 minutes (Note 3). The dropping funnel is then replaced by a thermometer, and the temperature of the solution is raised to 130° and held there 3 hours (Note 4). By this time the evolution of hydrogen chloride will have practically ceased.

The solution is cooled until its temperature is approximately that of the room, and 500 ml. of a mixture of equal parts of concentrated hydrochloric acid and water is added with stirring. The flask is then arranged for steam distillation and heated with a free flame while steam is passed into the reaction mixture until about 200 ml. of distillate is collected (Note 5). While hot, the mixture is placed in a large separatory funnel and the lower aqueous layer removed; the nitrobenzene layer is filtered through a Büchner funnel (Notes 6 and 7).

The nitrobenzene is then removed by vacuum distillation using a 2-l. Claisen flask, and the residue in the flask is distilled under diminished pressure; the fraction boiling at 180–195°/15 mm. is collected (Notes 8 and 9). The red-yellow oil, which solidifies on cooling, amounts to 128–176 g. (40–55%) and is sufficiently pure for some purposes (Note 10). A nearly white product can be obtained by dissolving the crude product in ether, shaking the ether solution with portions of 5% sodium hydroxide solution until no color appears in the aqueous layer, evaporating the ether, and recrystallizing the residue from a mixture of petroleum ether (b.p. 60–90°, Skellysolve B) and benzene (Note 11). The recrystallized product melts at 83–84°; the recovery is 80–85%.

## 2. Notes

1. Methyl acetoacetate has been used but insufficient data have been obtained as to the yield produced.

2. Commercial nitrobenzene is dried by distillation under reduced pressure until the distillate is clear. The residue is suitable for use without other treatment.

3. The aluminum chloride is added in 25–50 g. portions to the 2.1 l. of dry nitrobenzene contained in a 5-l. round-bottomed flask with stirring after each addition. The temperature may rise to 80–90° during the addition; occasional cooling of the flask under running water is necessary. After all the aluminum chloride has been added, the solution is cooled to room temperature. A small amount of aluminum chloride may settle to the bottom.

In one instance when the final cooling was omitted the temperature continued to rise and a large amount of hydrogen chloride was evolved. The residue in the flask was a thick paste. Addition of a portion of the paste to water caused nitrobenzene to separate. However, this batch was not suitable for condensation.

4. Below 100° the condensation does not take place; at 150° tar is formed and no coumarin can be isolated.

5. Some unchanged ester distils prior to the nitrobenzene; its removal aids in the subsequent separation of the two layers.

6. If a sufficiently large funnel is not available the separation may be done by dividing the solution in portions to suit the funnel available. If too much steam has condensed during the distillation, the aqueous layer may appear on top.

7. The tarry by-products clog filter paper immediately; a small quantity of filter aid may be used to promote the filtration. If the condensation has been satisfactory only a small amount of material will be retained, and this step may be omitted. Occasionally a considerable amount of lumpy, tarry material is removed; filtration is then more difficult, and the yield is lower. The tar, on distillation, yields no coumarin.

8. The recovered nitrobenzene, after being washed with water and dried as in Note 2, may be used again. The loss is from 400 to 700 ml.

9. Considerable tar remains in the distillation flask. The tar is best poured immediately into a flat pan of water or a sink where it solidifies to a hard brittle mass; that adhering to the walls of the flask is easily removed by adding 100–200 ml. of nitrobenzene to the flask and heating the solvent to boiling under atmospheric pressure.

10. According to the submitter, when quantities 3 times this size are used, the yield of distilled material is 38–50%.

11. The ratio of petroleum ether to benzene should be 8 to 2.

### 3. Methods of Preparation

4-Methylcoumarin is prepared by the condensation of phenol and acetoacetic ester. Concentrated sulfuric acid [1,2] and 73% sulfuric acid have been used.[3,4] The method given here was mentioned by Sethna, Shah, and Shah,[5] and the procedure is adapted from that of the same authors [6] for another coumarin derivative.

[1] Von Pechmann and Duisberg, *Ber.*, **16**, 2127 (1883).
[2] Von Pechmann and Kraft, *Ber.*, **34**, 421 (1901).
[3] Peters and Simonis, *Ber.*, **41**, 831 (1908).
[4] Fries and Volk, *Ann.*, **379**, 94, footnote 1 (1911).
[5] Sethna, Shah, and Shah, *Current Sci.*, **6**, 93 (1937) [*C.A.*, **32**, 549 (1938)].
[6] Sethna, Shah, and Shah, *J. Chem. Soc.*, **1938**, 228.

## METHYL PYRUVATE

### (Pyruvic acid, methyl ester)

$$CH_3COCO_2H + CH_3OH \xrightarrow{CH_3C_6H_4SO_3H} CH_3COCO_2CH_3 + H_2O$$

Submitted by A. Weissberger and C. J. Kibler.
Checked by C. S. Hamilton and R. F. Coles.

### 1. Procedure

A solution of 88 g. (1 mole) of freshly distilled pyruvic acid,[1] 128 g. (4 moles) of absolute methanol, 350 ml. of benzene, and 0.2 g. of *p*-toluenesulfonic acid is placed in a 1-l. round-bottomed flask connected through a ground-glass joint (Note 1) to a methyl ester column shown in Fig. 1 [2] (Note 2). The column is fitted at

METHYL PYRUVATE

[1] *Org. Syntheses* Coll. Vol. **I**, 475 (1943).
[2] Rahrs, *Synthetic Org. Chemicals*, Vol. XI, No. 1, The Eastman Kodak Company, February, 1938.

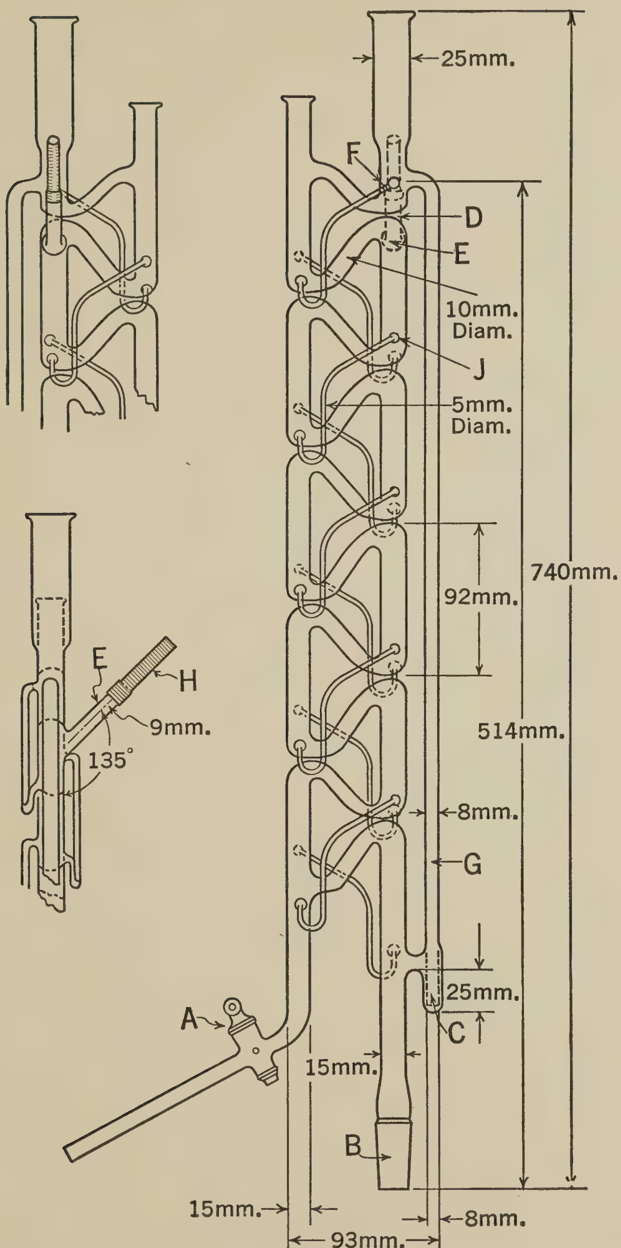

25mm.
F
D
E
10mm.
Diam.
J
5mm.
Diam.
92mm.
740mm.
514mm.
8mm.
G
25mm.
C
A
15mm.
B
15mm.
8mm.
93mm.
E
H
9mm.
135°

Fig. 1.

the top with a cold finger, thermometer, and an efficient condenser. The solution is refluxed vigorously using an oil bath maintained at 150–155°. The temperature at the top of the column is 59–60°. After refluxing overnight, the liquid in the lower bubbler becomes cloudy and separates into two layers. The lower layer is removed as fast as it is formed (i.e., every 20–30 minutes) throughout the day. Refluxing is continued overnight, and the next morning the lower layer is again removed until cloudiness persists in the upper bubblers (Note 3). The ester is then isolated by fractional distillation of the remaining liquid. The fraction boiling at 136–140° at atmospheric pressure is collected (Note 4). It weighs 66–73 g. (65–71%) (Notes 5 and 6).

## 2. Notes

1. A ground-glass joint is advisable on account of the long reflux period. Benzene attacks a rubber stopper, and pyruvic acid destroys cork.

2. The Clarke-Rahrs methyl ester column [2] is illustrated in Fig. 1. *A* is the stopcock, above which the aqueous phase collects and is drawn off as necessary. *B* is a standard-taper ground joint; *C* is a trap whose outside diameter is 12 mm. At *D* the space between the consecutive bubblers is shown. *E* is the thermometer tube, set in at an angle of about 45°; it carries a piece of rubber tubing *H* which holds the thermometer. *F* is a solid spot in the top return tube *only*, where that tube has been sealed off; the apparatus will not function without this seal. It should be pointed out that the upper ends of all the return tubes should terminate just above the bends, as shown at *J*; otherwise there will be too great a pressure due to the height of the liquid. The over-all length as given is not critical.

3. A total of about 300 ml. of liquid will have separated when cloudiness persists in the fourth and fifth bubblers. The liquid collected separates into two layers on cooling. It contains a trace of pyruvic acid.

4. A tarry residue of 10–17 g. is obtained. If an efficient column is not used in the distillation, the fore-runs will contain

5–10 g. of recoverable ester. The yield given is the total yield.

5. The difficulty in the preparation of methyl pyruvate is caused by the fact that this ester is very easily hydrolyzed and that the ester equilibrium is far on the side of the hydrolysis products.

6. Other methyl esters can be made by this procedure.

### 3. Methods of Preparation

Methyl pyruvate has been prepared from the silver salt of pyruvic acid and methyl iodide,[3] and from the free acid by the alcohol-vapor method without a catalyst.[4] Pyruvic esters have also been prepared by the dehydrogenation of lactic acid esters.[5]

## *o*-NITROBENZALDEHYDE

### (Benzaldehyde, *o*-nitro-)

$$o\text{-}O_2NC_6H_4CH_3 + 2(CH_3CO)_2O \xrightarrow{CrO_3} o\text{-}O_2NC_6H_4CH(OCOCH_3)_2 + 2CH_3COOH$$

$$o\text{-}O_2NC_6H_4CH(OCOCH_3)_2 + H_2O \xrightarrow{HCl} o\text{-}O_2NC_6H_4CHO + 2CH_3COOH$$

Submitted by S. M. Tsang, Ernest H. Wood, and John R. Johnson.
Checked by Lee Irvin Smith and J. W. Opie.

### 1. Procedure

A. *o-Nitrobenzaldiacetate.* In a 2-l. three-necked round-bottomed flask equipped with an effective mechanical stirrer and a thermometer, and surrounded by an ice bath, are placed

[3] Oppenheim, *Ber.*, **5**, 1051 (1872).
[4] Baker and Laufer, *J. Chem. Soc.*, **1937**, 1345.
[5] Hänssler, U.S. pat. 1,614,195 [*C.A.*, **21**, 746 (1927)].

600 g. (570 ml.) of glacial acetic acid, 565 ml. (612 g., 6 moles) of acetic anhydride, and 50 g. (0.36 mole) of *o*-nitrotoluene. To this solution is added slowly, with stirring, 156 g. (85 ml., 1.5 moles) of concentrated sulfuric acid. When the mixture has cooled to 5°, 100 g. (1 mole) of chromium trioxide is added in small portions at such a rate that the temperature does not rise above 10°; about 2 hours is required for the addition (Note 1). Stirring is continued for 5 hours after the chromium trioxide has been added (Note 2). The reaction mixture is poured into a large jar two-thirds filled with chipped ice, and cold water is added until the total volume is about 6 l. The mixture is then stirred vigorously for at least 15 minutes to promote solidification of the oily layer (Note 3). The oily solid is filtered with suction on a Büchner funnel, washed with cold water, and then stirred mechanically with 500 ml. of cold 2% sodium carbonate solution. The solid is then collected on a filter, washed with cold water, and dried in the air. The crude substance is digested with 150 ml. of petroleum ether (b.p. 60–70°) for 30 minutes, cooled, and filtered (Note 4). After having been dried in a vacuum desiccator, the product weighs 21–22 g. (23–24%) and melts at 87–88° (Note 5).

B. *o-Nitrobenzaldehyde.* A suspension of 51.6 g. of the diacetate in a mixture of 500 g. (272 ml.) of concentrated hydrochloric acid, 450 ml. of water, and 80 ml. of alcohol is stirred and refluxed for 45 minutes. The mixture is then cooled to 0°, and the solid is filtered with suction and washed with water (Notes 6 and 7). The crude product is purified by rapid steam distillation through a 100-cm. Allihn condenser into a cooled receiver. About 3.5 l. of distillate is collected during 30 minutes; the cooled distillate is filtered, and the *o*-nitrobenzaldehyde is dried in a desiccator over calcium chloride. It weighs 23.7 g. (74%) and melts at 44–45°.

## 2. Notes

1. Proper control of the temperature is very important during addition of the chromium trioxide. If the temperature rises very much, the reaction may become violent.

2. A hard, tarry mass forms during the later stages of this oxidation. For this reason stirring becomes increasingly difficult and a rather powerful motor must be used. After decantation of the liquid portion of the reaction mixture, ice and a little water (total volume 1 l. for the amounts of materials specified) are added to the reaction flask, and the mass is broken up with a spatula. The suspension is then combined with the mixture in the large jar.

3. It is essential that the oily layer should be stirred vigorously until it has solidified; otherwise large losses will be incurred during the subsequent filtration.

4. This treatment removes unchanged *o*-nitrotoluene.

5. The checkers have carried out this preparation using 3 times the amounts of material specified here. The percentage yields were the same.

6. In one run, the submitters substituted an equivalent amount of sulfuric acid for the hydrochloric acid, omitted the filtration, and steam-distilled the mixture directly. The yield of *o*-nitroaldehyde was 74.7%; this product also melted at 44–45°.

7. The crude aldehyde may be dried and then purified by distillation under reduced pressure. For this purpose, an ordinary Claisen flask is used. No fractionation is necessary; the distillation serves only to remove a small amount of tarry material. The boiling range is rather wide (120–144°/3–6 mm.) but the entire distillate (30 g. from 66 g. of the diacetate) solidifies and melts at 44–45°. The aldehyde may also be recrystallized, although with some loss. For this purpose 11 g. of the solid is dissolved in toluene (2–2.5 ml. per gram) at room temperature, the solution is diluted with petroleum ether (b.p. 30–60°; 7 ml. per ml. of solution) and cooled to −10° or below. The pale yellow needles weigh 9 g. and melt at 44–45°.

## 3. Methods of Preparation

*o*-Nitrobenzaldehyde has been prepared by action of oxides of nitrogen upon *o*-nitrobenzyl alcohol;[1] by oxidation of *o*-nitro-

[1] Cohen and Harrison, *J. Chem. Soc.*, **71**, 1057 (1897).

cinnamic acid or ester with permanganate or nitrous acid;[2] by oxidation of *o*-nitrophenylpyruvic acid with permanganate;[3] and from *o*-nitrotoluene by a number of methods. These include: action of isoamyl nitrite and sodium ethoxide, followed by hydrolysis of the resulting *o*-nitrobenz-*anti*-aldoxime with concentrated hydrochloric acid;[4] direct action of a number of oxidizing agents including potassium dichromate and sulfuric acid,[5] manganese dioxide,[6] nickel oxide,[7] and cerium oxide;[8] action of mercury oxide in the presence of alkali, followed by hydrolysis of the resulting *o*-nitrobenzalmercurioxide with nitrous or nitric acid;[9] and action of chromic acid in acetic acid and acetic anhydride, followed by hydrolysis of the resulting *o*-nitrobenzaldiacetate.[10] *o*-Nitrobenzaldehyde is also formed, along with much *m*-nitrobenzaldehyde, by direct nitration of benzaldehyde.[11]

[2] Friedländer and Henriques, *Ber.*, **14**, 2803 (1881).

[3] Reissert, *Ber.*, **30**, 1042 (1897).

[4] Lapworth, *J. Chem. Soc.*, **79**, 1274 (1901); Farbwerke vorm. Meister, Lucius, and Brüning, Ger. pat. 107,095 (*Chem. Zentr.*, **1900**, I, 886).

[5] Lauth, *Bull. soc. chim.*, (3) **31**, 133 (1904).

[6] Gilliard, Monnet, and Cartier, Ger. pat. 101,221 (*Chem. Zentr.*, **1899**, I, 959); Badische Anilin- u. Sodafabr., Ger. pat. 175,295 (*Chem. Zentr.*, **1906**, II, 1589).

[7] Badische Anilin- u. Sodafabr., Ger. pat. 127,388 (*Chem. Zentr.*, **1902**, I, 150).

[8] Farbwerke vorm. Meister, Lucius, and Brüning, Ger. pat. 174,238 (*Chem. Zentr.*, **1906**, II, 1297).

[9] Reissert, *Ber.*, **40**, 4216, 4220 (1907); Ger. pat. 186,881 (*Chem. Zentr.*, **1907**, I, 1295).

[10] Thiele and Winter, *Ann.*, **311**, 356 (1900).

[11] Friedländer and Henriques, *Ber.*, **14**, 2801 (1881).

## *p*-NITROBENZYL ACETATE

**(Acetic acid, *p*-nitrobenzyl ester)**

$$p\text{-}O_2NC_6H_4CH_2Cl + NaOCOCH_3 \rightarrow p\text{-}O_2NC_6H_4CH_2OCOCH_3 + NaCl$$

Submitted by W. W. Hartman and E. J. Rahrs.
Checked by R. L. Shriner and Charles Russell.

### 1. Procedure

A mixture of 250 g. (1.46 moles) of *p*-nitrobenzyl chloride, 225 g. (2.74 moles) of fused sodium acetate, and 375 g. (6.25 moles) of glacial acetic acid is refluxed for 8 to 10 hours in a 2-l. flask heated by an oil bath, the temperature of which is maintained at 160–170° (Note 1). After this time the bath is allowed to cool to about 125°, and the acetic acid is removed by distillation under reduced pressure. Care must be taken not to reduce the pressure too rapidly in the early stages of the distillation. As the distillation slows down, the pressure is further reduced until it reaches 50 mm. or lower, and the temperature is slowly raised to 160°. From 2.5 to 3 hours is required for the complete removal of the acetic acid. About 500 ml. of water is added, and the hard cake is broken up with a stirring rod (Note 2).

The entire contents of the flask are then transferred to a 1.5-l. beaker and stirred with a mechanical stirrer for about 30 minutes or long enough to break up all the lumps. The finely divided material is filtered on a Büchner funnel and washed with 200 ml. of cold water. The above process of washing, stirring, and filtering is repeated twice. The product is then transferred to a 1.5-l. beaker, and 500 ml. of methanol is added and heated to boiling in order to effect solution. The hot solution is filtered through a heated Büchner funnel and allowed to cool slowly. When the solution has cooled to 20°, the product is collected on a filter and air-dried. This first crop consists of yellow needles which melt at 74–77° and weigh 215–225 g. The filtrate is

evaporated to 100 ml. and cooled. An additional 25–30 g. of solid separates. Both crops are again washed with cold water and recrystallized from 500 ml. of hot methanol. The first crop from this second crystallization weighs 210–218 g. and melts at 77–78°. Evaporation of the filtrate to 100 ml. and cooling yield an additional 15–18 g. of acetate which is purified by recrystallization from methanol; about 12 to 15 g. of product is obtained. The combined yield of pale yellow crystals which melt at 77–78° amounts to 222–233 g. (78–82%).

## 2. Notes

1. *p*-Nitrobenzyl chloride obtained from the Eastman Kodak Company was used.

2. The hard cake may be removed by the addition of 500 ml. of boiling water; the ester melts and forms an oily layer. The molten ester solidifies in small lumps when the flask is cooled rapidly in an ice bath while the molten mixture is stirred vigorously. Purification in this manner by repeating the process 2 or 3 times does not seem to produce better results than purification with cold water.

## 3. Methods of Preparation

*p*-Nitrobenzyl acetate has been prepared by the action of alcoholic potassium acetate on *p*-nitrobenzyl chloride [1] or bromide [2] and by the nitration of benzyl acetate.[3]

[1] Grimaux, *Zeit. für Chem.*, **1867**, 562.
[2] Reid, *J. Am. Chem. Soc.*, **39**, 130 (1917).
[3] Beilstein and Kuhlberg, *Ann.*, **147**, 340 (1868).

# *p*-NITROBENZYL ALCOHOL

## (Benzyl alcohol, *p*-nitro)

$$p\text{-}O_2NC_6H_4CH_2OCOCH_3 + NaOH \rightarrow p\text{-}O_2NC_6H_4CH_2OH + CH_3CO_2Na$$

Submitted by W. W. HARTMAN and E. J. RAHRS.
Checked by R. L. SHRINER and CHARLES RUSSELL.

### 1. Procedure

A solution of 218 g. (1.12 moles) of *p*-nitrobenzyl acetate (p. 79) in 500 ml. of hot methanol is prepared in a 2-l. flask. To the hot solution is added 380 g. (1.43 moles) of a 15% solution of sodium hydroxide. The alkali should be added slowly at first with shaking to prevent too vigorous boiling. After standing for 5 minutes, the mixture is poured with vigorous hand stirring into 4.5 kg. of a mixture of cracked ice and water. The precipitate is collected on a Büchner funnel and recrystallized from 3 to 3.7 l. of hot water with the aid of 15 g. of Norite. The alcohol is dried at 60° to 65° in an oven for several hours and bottled (Note 1). The yield of slender, nearly colorless needles amounts to 110–121 g. (64–71%); the product melts at 92–93° (Note 2).

### 2. Notes

1. The product turns yellow if it is spread out to dry in the air.

2. The submitters report that *p*-iodobenzyl alcohol can be prepared in a similar manner, and that it is unnecessary to isolate the acetate. A mixture of 148 g. of *p*-iodobenzyl bromide, 52 g. of potassium acetate, and 750 ml. of 95% ethanol is refluxed for 8 hours, cooled, and filtered from the salt. To the filtrate is added 33.6 g. of potassium hydroxide, and the solution is refluxed

for 6 hours. It is then diluted with 2 l. of water, and the oil taken up in 500 ml. of chloroform. After concentration to 150 ml. and chilling, *p*-iodobenzyl alcohol crystallizes. It is filtered and the solid rinsed with petroleum ether; the rinse added to the mother liquor causes the separation of an additional amount of *p*-iodobenzyl alcohol. The combined yield is 95–100 g. (81–86%); the product melts at 70–72°.

### 3. Methods of Preparation

*p*-Nitrobenzyl alcohol has been secured by the oxidation of *p*-nitrotoluene electrolytically [1] or chemically,[2] and by the hydrolysis of the acetate.[3,4] *p*-Iodobenzyl alcohol has been prepared by the hydrolysis of *p*-iodobenzyl bromide and *p*-iodobenzyl acetate.[5,6]

## PHENYLMETHYLGLYCIDIC ESTER

### (Glycidic acid, β-methyl-β-phenyl-, ethyl ester)

$$C_6H_5COCH_3 + ClCH_2CO_2C_2H_5 + NaNH_2 \rightarrow$$
$$C_6H_5\underbrace{C(CH_3)\text{—}CH}_{O}CO_2C_2H_5 + NaCl + NH_3$$

Submitted by C. F. H. Allen and J. Van Allan.
Checked by Nathan L. Drake and Carl Blumenstein.

### 1. Procedure

To a mixture of 120 g. (118.5 ml., 1 mole) of acetophenone (Note 1), 123 g. (109 ml., 1 mole) of ethyl chloroacetate, and

[1] Elbs, *Ber.* (Ref.), **29**, 1122 (1896).
[2] Dieffenbach, Ger. pat. 214,949 [*Frdl.*, **9**, 156 (1908–10)].
[3] Beilstein and Kuhlberg, *Ann.*, **147**, 343 (1868).
[4] Basler, *Ber.*, **16**, 2715 (1883).
[5] Mabery and Jackson, *Ber.*, **11**, 56 (1878).
[6] Jackson and Mabery, *Am. Chem. J.*, **2**, 251 (1880).

200 ml. of dry benzene in a 1-l. three-necked round-bottomed flask, fitted with a stirrer and low-temperature thermometer, is added, over a period of 2 hours, 47.2 g. (1.2 moles) of finely pulverized sodium amide.[1] The temperature is kept at 15–20° by external cooling (Note 2). After the addition has been completed, the mixture is stirred for 2 hours at room temperature, and the reddish mixture is poured upon 700 g. of cracked ice, with hand stirring. The organic layer is separated and the aqueous layer extracted once with 200 ml. of benzene. The combined benzene solutions are washed with three 300-ml. portions of water, the last one containing 10 ml. of acetic acid. The benzene solution is dried over 25 g. of anhydrous sodium sulfate, filtered, the drying agent rinsed with a little dry benzene, and, after removal of the solvent, the residue is fractionated *in vacuo*, using a modified Claisen flask. The fraction boiling at 107–113°/3 mm. is collected separately and used for the preparation of hydratropaldehyde (p. 87). Redistillation yields a product which boils at 111–114°/3 mm. (Note 3). The yield is 128–132 g. (62–64%) (Note 4).

## 2. Notes

1. The Practical grades of ketone and ester were used.
2. The reaction is strongly exothermic, and much ammonia is evolved.
3. Other boiling points are 272–275°/760 mm. with decomposition; 153–159°/20 mm.; and 147–149°/12 mm.
4. There are several side reactions which reduce the yield. There are always unchanged ketone and ester in the low-boiling fraction, and also some chlorocinnamic ester.

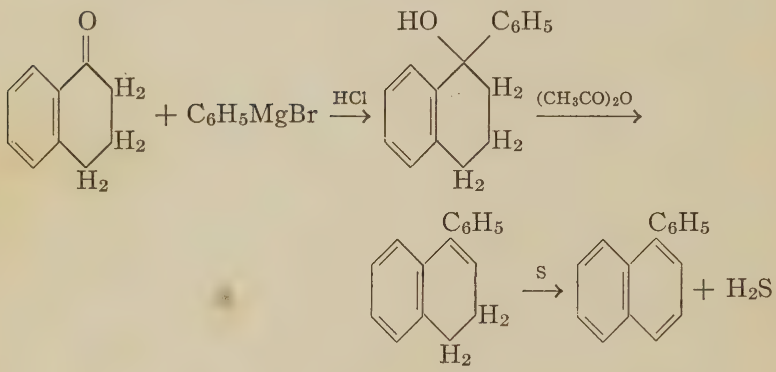
[1] *Org. Syntheses*, **20**, 86 (1940).

### 3. Methods of Preparation

This is an example of a general reaction by which haloesters are condensed with ketones by means of sodium,[2] sodium ethoxide,[3,4] or sodium amide.[5,6,7]

## 1-PHENYLNAPHTHALENE

### (Naphthalene, 1-phenyl-)



Submitted by Richard Weiss.
Checked by C. F. H. Allen and F. P. Pingert.

### 1. Procedure

A. *1-Phenyldialin.* A solution of phenylmagnesium bromide is prepared in the usual manner [1] from 11 g. (0.45 gram atom) of

[2] Erlenmeyer, *Ann.*, **271**, 161 (1892).

[3] Darzens, *Compt. rend.*, **139**, 1215 (1904).

[4] Dutta, *J. Indian Chem. Soc.*, 18, 235 (1941) [*C.A.*, **36**, 761 (1942)].

[5] Claisen and Feyerabend, *Ber.*, **38**, 702 (1905).

[6] I. G. Farbenind. A.-G., Ger. pat. 591,452 [*Frdl.*, **19**, 288 (1934)] [*C.A.*, **28**, 2367 (1934)].

[7] I. G. Farbenind. A.-G., Ger. pat. 602,816 [*Frdl.*, **20**, 217 (1935)] [*C.A.*, **29**, 1438 (1935)].

1-PHENYLNAPHTHALENE

[1] *Org. Syntheses* Coll. Vol. **I**, 226 (1941).

magnesium, 75 g. (0.48 mole) of bromobenzene, and 175 ml. of ether. As soon as the metal has reacted, a solution of 58.4 g. (0.4 mole) of $\alpha$-tetralone [2] in 60 ml. of ether is added from a dropping funnel as rapidly as possible so that vigorous refluxing is maintained; about 30 minutes is required. The reaction mixture is then heated under reflux for an additional 30 minutes and allowed to stand for 1 hour. The magnesium complex is decomposed by about 250 g. of ice and 40 ml. of concentrated hydrochloric acid. The ether layer is separated and distilled with steam to remove impurities (Note 1); about 6 hours is necessary, and approximately 4.5 l. of distillate is collected. The heavy residual oil is separated from the water, and 80 ml. of ether and 10 g. of calcium chloride are added. After 4 to 5 minutes, the calcium chloride is removed by filtration, and the ether is driven off by distillation on a steam bath. Twenty milliliters of acetic anhydride is then added, and the flask and contents are heated in a steam bath (Note 2) for 20–25 minutes. The mixture is finally distilled *in vacuo* through a 15-in. Widmer column [3] (Note 3). The fraction which boils at 135–140°/2 mm. is collected; the yield is 35–40 g. (42–48%).

B. *1-Phenylnaphthalene.* A mixture of 6 g. (0.18 mole) of powdered sulfur and 35 g. (0.17 mole) of 1-phenyldialin in a 200-ml. Claisen flask having a modified side arm [4] is heated for 30 minutes in a metal bath the temperature of which is 250–270° (Note 4). At the end of this time the evolution of hydrogen sulfide will have ceased. The heavy oil (Note 5) is then distilled from the same flask; the yield is 32–33 g. (91–94%); the boiling range of the product is 134–135°/2 mm. or 189–190°/12 mm. (Notes 6 and 7).

## 2. Notes

1. Steam distillation removes unused bromobenzene, biphenyl, etc.

2. The reaction is best carried out in a 500-ml. Erlenmeyer

[2] *Org. Syntheses*, **20**, 94 (1940).

[3] *Org. Syntheses*, **20**, 53 (1940).

[4] *Org. Syntheses* Coll. Vol. **I**, 130 (1941).

flask or beaker which can be lowered into the steam pot and held by a cloth wrap.

3. If a fractionating column is not used, several distillations are necessary to secure a product with the boiling range given. When this distillation is done as described, subsequent operations are facilitated, and a column is not required for the final distillation of the hydrocarbon. Ebullition tubes are desirable in both distillations.

4. The temperature inside the flask should be 250°.

5. Significant amounts of hydrocarbon are lost with each change of flask. For this reason it is advisable to perform the dehydrogenation and distillation in the same flask.

6. Sometimes the hydrocarbon is blue, probably owing to traces of an azulene. The contaminant is easily removed by dissolving the hydrocarbon in an equal volume of hexane or petroleum ether and shaking this solution with an equal volume of 85% syrupy phosphoric acid until the color has been removed. The hydrocarbon is then obtained on evaporation of the solvent; it does not need redistillation.

7. The over-all yield is 40%, based on the α-tetralone.

## 3. Methods of Preparation

1-Phenylnaphthalene has been prepared by the reaction of α-halonaphthalenes with mercury diphenyl [5] or with benzene in the presence of aluminum chloride,[5] and by means of the Grignard synthesis, starting with either bromobenzene, cyclohexyl chloride, and α-tetralone [6,7] or with α-bromonaphthalene and cyclohexanone.[6,8,9] Dehydrogenation of the reduced naphthalene has been accomplished by the use of sulfur,[6] bromine,[8] platinum black, or selenium.[7] The formation of the hydrocar-

[5] Chattaway, *J. Chem. Soc.*, **63**, 1187 (1893).

[6] Weiss and Woidich, *Monatsh.*, **46**, 455 (1925).

[7] Cook and Lawrence, *J. Chem. Soc.*, **1936**, 1432.

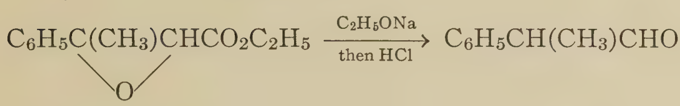
[8] Sherwood, Short, and Clausfield, *J. Chem. Soc.*, **1932**, 1834.

[9] Veselý and Štursa, *Collection Czechoslov. Chem. Commun.*, **5**, 344 (1933) [*C.A.*, **28**, 144 (1934)].

bon through the diazo reaction [10, 11, 12, 13] appears to be less attractive than the method described.

## α-PHENYLPROPIONALDEHYDE

### (Hydratropaldehyde)



Submitted by C. F. H. ALLEN and J. VAN ALLAN.
Checked by NATHAN L. DRAKE and CARL BLUMENSTEIN.

### 1. Procedure

An alcoholic solution of sodium ethoxide is prepared in a 1-l. round-bottomed flask from 15.5 g. (0.67 gram atom) of sodium and 300 ml. of absolute ethanol (Note 1). One hundred thirty-three grams (0.64 mole) of phenylmethylglycidic ester (p. 82) is then added to this solution slowly and with shaking. The flask is then cooled externally to 15°, and 15 ml. of water is slowly added; considerable heat is evolved, and the sodium salt soon begins to separate. After the mixture has stood overnight, the salt is filtered by suction and rinsed with one 50-ml. portion of alcohol and a similar amount of ether. The dried salt weighs 102–108 g. (80–85%) and melts at 255–256° with decomposition.

The salt is added to a dilute solution of hydrochloric acid prepared by mixing 300 ml. of water and 56 ml. of concentrated acid (sp. gr. 1.18); the acid should be contained in a 1-l. flask under a reflux condenser. The mixture is warmed gently, whereupon carbon dioxide is evolved and an oil separates. The flask is heated on a steam bath for 1.5 hours, and the oil is then extracted

[10] Grieve and Hey, *J. Chem. Soc.*, **1938**, 113.
[11] Water, *J. Chem. Soc.*, **1939**, 864.
[12] Hodgson and Marsden, *J. Chem. Soc.*, **1940**, 208.
[13] Bachmann and Hoffman, *Organic Reactions*, Vol. II, p. 248, John Wiley & Sons, 1944.

from the cooled mixture with 150 ml. of benzene. The extract is washed once with 200 ml. of water and distilled *in vacuo*, using an ordinary 500-ml. Claisen flask. The hydratropaldehyde distils at 90–93°/10 mm. or 73–76°/4 mm. (oil bath at 120–130°), leaving only a slight residue (3–5 g.). The yield is 56–60 g. (65–70%) (Notes 2 and 3).

## 2. Notes

1. The metal is placed in the flask, and the alcohol is added through the condenser as fast as refluxing will allow.[1]
2. The generality of this reaction is limited only by the availability of the glycidic esters.
3. The 2,4-dinitrophenylhydrazone forms yellow prisms which melt at 135°.

## 3. Methods of Preparation

Hydratropaldehyde has been prepared by hydrolysis of phenylmethylglycidic ester,[2,3,4] by chromyl chloride oxidation of cumene,[5] by the elimination of halogen acid or water from halohydrins or glycols,[6,7,8] and by the distillation at ordinary pressure of methylphenylethylene oxide.[9,10]

[1] *Org. Syntheses*, **23**, 18, Note 1 (1943).
[2] Claisen, *Ber.*, **38**, 703 (1905).
[3] I. G. Farbenind. A.-G., Ger. pat. 602,816 [*Frdl.*, **20**, 217 (1935)].
[4] Dutta, *J. Indian Chem. Soc.*, **18**, 235 (1941) [*C.A.*, **36**, 161 (1942)].
[5] v. Miller and Rohde, *Ber.*, **24**, 1359 (1889).
[6] Bougault, *Ann. chim. phys.*, (7) **25**, 548 (1902).
[7] Tiffeneau, *Bull. soc. chim.*, (3) **27**, 643 (1902); *Compt. rend.*, **134**, 846 (1902); **137**, 1261 (1903); **142**, 1538 (1906); *Ann. chim. phys.*, (8) **10**, 353 (1907).
[8] Stoermer, *Ber.*, **39**, 2298 (1906).
[9] Klages, *Ber.*, **38**, 1971 (1905).
[10] Tiffeneau, *Compt. rend.*, **140**, 1459 (1905); *Ann. chim. phys.*, (8) **10**, 192 (1907).

# SELENOPHENOL

## (Benzeneselenol)

$$C_6H_5MgBr \xrightarrow[\text{then HCl}]{\text{Se}} C_6H_5SeH + MgClBr$$

Submitted by Duncan G. Foster.
Checked by C. F. H. Allen and H. W. J. Cressman.

### 1. Procedure

*Most selenium compounds are toxic, and many have a vile odor. It is frequently advisable to work with them on alternate days. All manipulations should be done in a good hood. Rubber gloves should be worn, and it is well to keep the window of the hood down so that the glass is between the apparatus and the face of the operator.*

*Hydrogen selenide, a possible by-product, is very toxic, being comparable with hydrogen cyanide. Its accidental inhalation in small amounts may produce a sore throat.*

A 500-ml. three-necked round-bottomed flask is fitted with an efficient reflux condenser, a glycerol-sealed mechanical stirrer,[1] a dropping funnel, and a gas inlet tube extending nearly to the blades of the stirrer (Note 1). An absorption train,[2] with the addition in *J* of a safety tube which extends nearly to the bottom, is connected to the upper end of the reflux condenser (Note 2). A 2-cm. layer of water in *J* allows it to serve as a bubble counter; *K* is one-third filled with a 50% potassium hydroxide solution. The entire apparatus is set up in subdued light in a hood and swept with dry hydrogen (Notes 3 and 4). Phenylmagnesium bromide is prepared in the flask by the usual procedure [3] from 78.5 g. (0.5 mole) of bromobenzene, 12 g. (0.5 gram

[1] *Org. Syntheses*, **21**, 40 (1941).
[2] *Org. Syntheses* Coll. Vol. **I**, 266, Fig. 15 (1941).
[3] *Org. Syntheses* Coll. Vol. **I**, 226 (1941).

atom) of magnesium, and 500 ml. of dry ether. The dropping funnel is then replaced by an addition flask [4] which contains 38 g. (0.48 gram atom) of dry powdered black selenium (Note 5). The solution is warmed sufficiently to bring about gentle refluxing, and the selenium is then added gradually over a period of 30 minutes at such a rate as to maintain gentle refluxing without heating. Stirring is continued for an additional 30 minutes (Note 6).

The contents of the flask are then poured upon 600 g. of cracked ice, and, with hand stirring, 75 ml. of hydrochloric acid (sp. gr. 1.18) is added. The cold mixture is now filtered through glass wool in an ordinary funnel into a 2-l. separatory funnel. The aqueous layer is separated and extracted once with 250 ml. of ether (Note 7). The combined extract and main product are dried over 30 g. of calcium chloride, the ether is removed on a steam bath, and the residue is distilled using a 500-ml. modified Claisen flask.[5] The selenophenol is collected at 57–59°/8 mm. or 84–86°/25 mm.; the yield is 43–54 g. (57–71%) (Notes 6 and 9 through 14). The product should be sealed at once in a glass vial (Note 8).

## 2. Notes

1. Dry hydrogen or dry nitrogen may be used. The gas must be oxygen-free. Hydrogen tends to decrease the amount of oxidation to diselenide.

2. The submitter used a simpler train consisting of two small wide-mouthed bottles in series closed by stoppers bearing the necessary inlet and outlet tubes constructed of 10-mm. or larger glass tubing. In each flask was a shallow layer of 50% potassium hydroxide solution; the outlet tube of the first bottle extended nearly to the surface of the solution and dipped *below* the surface of the solution in the second bottle.

3. Most selenium compounds are affected by sunlight, and many by any bright light. It is often essential to use amber glassware or to wrap the flasks in light-proof paper.

[4] *Org. Syntheses*, **23**, 59 (1943).

[5] *Org. Syntheses* Coll. Vol. **I**, 130 (1941).

4. Selenium compounds which contain an —SeH group are easily oxidizable in the air to diselenides. It is advantageous to replace the air by an inert gas, and to work as rapidly as possible.

5. The selenium is dried overnight in a vacuum desiccator over concentrated sulfuric acid.

6. The higher yields of selenophenol are favored by exclusion of air, rapid stirring, and not too rapid addition of selenium.

7. An alternative procedure is to extract the selenophenol by sodium hydroxide solution, and subsequently to acidify and extract the liberated substance. The yield of selenophenol is not improved by employing such a procedure, but it may be of value with some compounds.

8. The selenophenol is water-white but rapidly turns yellow in contact with the air.

9. The residue in the still (or alkali-insoluble material in the ether layer if Note 6 has been employed) contains diphenyl selenide (b.p. 167°/16 mm.) and diphenyl diselenide (m.p. 63°). It can be separated by a combination of distillation and crystallization from alcohol, but the amounts are small, and, unless the residues from several runs are combined, the procedure is not economical.

10. This is a general reaction. It can be used for preparing other selenophenols whenever the desired Grignard reagent can be obtained. The submitter has made the three selenocresols, *p*-bromophenylselenophenol, and *n*-butylselenol by this procedure. He has also obtained thiophenols by the substitution of sulfur for selenium.

11. The submitter has synthesized nine alkyl phenyl selenides in yields of 85–95% by treating alcohol solutions of the sodium salt (the selenophenol is dissolved in the calculated amount of 50% aqueous sodium hydroxide diluted with alcohol) with the appropriate alkyl halide or sulfate.

12. Many selenophenols are more advantageously prepared by hydrolysis of the aryl selenocyanate.

13. It is well to have a hot sulfuric-nitric acid cleaning bath in the same hood, so that apparatus need not be handled in the open laboratory. The large separatory funnel is conveniently

cleaned by pouring into it 50 ml. of concentrated nitric acid. After a few minutes, the acid reacts violently with selenides remaining on the sides. The oxides of nitrogen produced effectively clean the funnel, which can then be rinsed with water.

14. Water-soluble selenium compounds are poured down the sink in the hood and flushed with much water. Rubber stoppers and gloves can be freed from toxic compounds by soaking them for a few minutes in bromine or chlorine water and then in dilute sodium hydroxide solution.

### 3. Methods of Preparation

Selenophenol has been prepared from selenium tetrachloride and benzene in the presence of anhydrous aluminum chloride,[6] and by the procedure described,[7] which is a development of Taboury's.[8]

## SORBIC ACID

$$CH_3CH{=}CHCHO + H_2C(CO_2H)_2 \xrightarrow{\text{Pyridine}} CH_3CH{=}CHCH{=}CHCO_2H + CO_2 + H_2O$$

Submitted by C. F. H. Allen and J. Van Allan.
Checked by C. S. Hamilton and R. A. Alberty.

### 1. Procedure

A mixture of 80 g. (93.2 ml., 1.14 moles) of crotonaldehyde (b.p. 102–103°), 120 g. (1.15 moles) of malonic acid [1] (m.p. 134–135°), and 120 g. (122 ml., 1.52 moles) of pyridine (b.p. 113–

[6] Chabrie, *Bull. soc. chim.*, (2) **50**, 133 (1888); *Ann. chim. phys.*, (6) **20**, 229 (1890).

[7] Foster and Brown, *J. Am. Chem. Soc.*, **50**, 1184 (1928).

[8] Taboury, *Bull. soc. chim.*, (3) **29**, 762 (1903); *Ann. chim. phys.*, (8) **15**, 36, 38 (1908).

SORBIC ACID

[1] *Org. Syntheses*, **18**, 50 (1938).

115°) is heated for 3 hours in a 1-l. flask on a steam bath under a reflux condenser. At the end of this period the evolution of carbon dioxide will have practically ceased. The flask and contents are then cooled in ice, and a solution of 42.5 ml. (0.76 mole) of concentrated sulfuric acid in 100 ml. of water is added with shaking. Most of the sorbic acid separates at once; the remainder is obtained by chilling the solution in an ice bath for 3 hours. The crude acid is filtered by suction and washed once with a small amount of ice water; it is recrystallized at once from 250 ml. of boiling water. The purified acid, which separates on standing overnight in the ice chest, is filtered; it melts at 134°. The yield is 36–41 g. (28–32%) (Notes 1, 2, and 3).

## 2. Notes

1. The submitters have found that the percentage yield is the same when double the above quantities are used.

2. This is an example of a general reaction. If acetic acid is used as a solvent, the substituted malonic acids can be secured, whereas organic bases facilitate the loss of carbon dioxide. The product is generally a mixture from which but a single substance can be isolated.

3. The use of simple aldehydes gives better yields of unsaturated acids; this is especially noticeable when aromatic aldehydes are employed.[2] Mixtures of $\alpha,\beta$- and $\beta,\gamma$-unsaturated acids have been reported when aliphatic aldehydes and certain basic catalysts are used.[3,4]

[2] Pandya, K. A., and Pandya, R. B., *Proc. Indian Acad. Sci.*, **14A**, 112 (1941) [*C.A.*, **36**, 1599 (1942)].

[3] Auwers, *Ann.*, **432**, 58 (1923).

[4] Boxer and Linstead, *J. Chem. Soc.*, **1931**, 740.

### 3. Methods of Preparation

Sorbic acid has been prepared from crotonaldehyde [5] or aldol [6] and malonic acid in pyridine solution; by hydrogen peroxide oxidation of the condensation product of crotonaldehyde and pyruvic acid; [7] and by the action of alkali on 3-hydroxy-4-hexenoic acid,[8,9] $\beta,\delta$-disulfo-*n*-caproic acid,[10] and parasorbic acid.[11,12]

## UNDECYL ISOCYANATE

$$n\text{-}C_{11}H_{23}COCl + NaN_3 \longrightarrow n\text{-}C_{11}H_{23}CON_3 \xrightarrow{\text{heat}} n\text{-}C_{11}H_{23}NCO + N_2$$

Submitted by C. F. H. Allen and Alan Bell.
Checked by Nathan L. Drake and John Sterling.

### 1. Procedure

In a 1-l. three-necked flask, equipped with a stirrer and a thermometer and immersed in an ice bath, is placed 46 g. (0.7 mole) of sodium azide (Note 1) in 150 ml. of water. A mixture of 109 g. (0.5 mole) of lauroyl chloride (b.p. 134–137°/11 mm.) and 150 ml. of acetone is then added from a separatory funnel to the well-stirred solution of the azide at such a rate that the temperature remains at 10–15°. After the mixture has been stirred at this temperature for an hour, the stirrer is stopped and, when the layers have separated, the lower water layer is removed care-

[5] Doebner, *Ber.*, **33**, 2140 (1900).
[6] Riedel, *Ann.*, **361**, 90 (1908).
[7] Smedley and Lubrzynska, *Biochem. J.*, **7**, 370 (1913).
[8] Jaworski, *J. Russ. Phys. Chem. Ges.*, **35**, 274 (1903) [*Chem. Zentr.*, **1903**, II, 555].
[9] Jaworski and Reformatski, *Ber.*, **35**, 3636 (1902).
[10] Notebohn, *Ann.*, **412**, 77 (1916).
[11] Hofmann, *Ann.*, **110**, 132 (1859).
[12] Doebner, *Ber.*, **27**, 351 (1894).

fully by suction through a glass capillary tube (Note 2). The upper layer is then added slowly to 500 ml. of benzene which has been warmed to 60° (Note 3). A rather rapid evolution of gas results, and the mixture is kept at 60–70° (Note 4) until no more nitrogen is evolved; the conversion of azide to isocyanate requires about an hour. The solution is filtered to remove any insoluble matter, and the benzene is removed by distillation from a modified Claisen flask. Distillation of the residue yields 80–85 g. of ester (81–86%) (Notes 5 and 6).

## 2. Notes

1. A Practical grade of sodium azide such as that obtained from the Eastman Kodak Company is satisfactory.
2. It is important that the water be removed as completely as possible before the azide is added to the warm benzene. Failure to remove the water causes formation of the *sym.*-disubstituted urea during decomposition of the azide. If the water is separated carefully, there will be no need to filter the benzene solution before the final distillation.
3. If the azide is added too rapidly, the solution may froth over; it is best to carry out this reaction in a 1-l. beaker.
4. The heat of reaction is usually sufficient to maintain the temperature at 60–70°.
5. On redistillation all the product boils at 103°/3 mm. A second distillation is unnecessary; the original ester is pure enough for all practical purposes.
6. This method is a general one for the preparation of isocyanates.[1]

## 3. Method of Preparation

This procedure is one used by Schröter for preparing alkyl isocyanates.[1]

[1] Schröter, *Ber.*, **42**, 3356 (1909).

# VINYLACETIC ACID

## (β-Butenoic acid)

$$CH_2{=}CHCH_2CN + 2H_2O + HCl \rightarrow CH_2{=}CHCH_2CO_2H + NH_4Cl$$

Submitted by EDWARD RIETZ.
Checked by C. F. H. ALLEN and JAMES VAN ALLAN.

### 1. Procedure

In a 500-ml. flask attached to a reflux condenser is placed a mixture of 67 g. (104 ml., 1 mole) of allyl cyanide [1] (Note 1) and 100 ml. (1.2 moles) of concentrated hydrochloric acid (sp. gr. 1.19). The mixture is heated by a small flame and is shaken frequently. After 7 to 8 minutes, the reaction begins, a voluminous precipitate of ammonium chloride appears, the temperature rises rapidly, and the mixture refluxes. After 15 minutes the flame is removed, 100 ml. of water is added, and the upper layer of the acid is separated (Note 2). The aqueous layer is extracted with two 100-ml. portions of ether. The extracts and the acid are combined and distilled. Most of the ether is removed at atmospheric pressure (Notes 3, 4, and 5), and the remainder is removed as the pressure is diminished. The acid is collected at 70–72°/9 mm. after a fore-run of approximately 40 g. The yield of crude acid is 50–53 g. (52–62%) (Note 5).

Although this product is pure enough for most purposes, it contains small amounts of by-products which cannot be removed by distillation. Further purification is accomplished by the following procedure: In a 250-ml. three-necked round-bottomed flask fitted with a stirrer, a small dropping funnel, and a thermometer for reading low temperatures, 24 g. of sodium hydroxide is dissolved in 80 ml. of water. While the temperature *of the solution* is maintained at 8–15° by external cooling, 45 g. (40.5 ml.)

[1] *Org. Syntheses* Coll. Vol. **I,** 46 (1941).

of the impure vinylacetic acid is added; this operation requires 25 minutes. This solution is transferred to a 600-ml. conical separatory funnel and extracted with 50 ml. of chloroform (Notes 6 and 7). The alkaline solution is *immediately* transferred to a 1-l. beaker, and 300 ml. of dilute sulfuric acid (Notes 8 and 9) is added with stirring. This acid solution is *at once* extracted with three 100-ml. portions of chloroform (Notes 7 and 10). The solvent is then removed by distillation, first at atmospheric pressure and then at reduced pressure, from a 200-ml. modified Claisen flask.[2] The residue is distilled under reduced pressure. Almost all the material boils at 69–70°/12 mm. (163°/760 mm.). The recovery is 30–33 g. (75–82%) (Note 11).

## 2. Notes

1. An improved procedure for preparation of allyl cyanide (3-butenenitrile) is as follows: In a dry (washed with absolute alcohol and absolute ether) 500-ml. three-necked flask, equipped with a mechanical stirrer [3] and a 90-cm. bulb condenser set vertically and protected by a calcium chloride tube, are placed 85 g. of dry cuprous cyanide (commercial, or prepared as previously described;[4] dried for 72 hours in an oven at 110° just before use), 0.25 g. of potassium iodide, and 72.5 g. of allyl chloride (dried over calcium chloride and freshly distilled; b.p. 45–47°). The stirrer is started, and the mixture is heated on a water bath. After about 6 hours the reaction is substantially complete, as indicated by cessation of the refluxing; heating is continued for 1 hour beyond this point. With larger runs it may be necessary to moderate the reaction by removing the water bath when vigorous refluxing sets in. This usually occurs about 3 to 5 hours after heating is started. Runs of the size described do not require any special attention. The water bath is replaced by an oil bath, the condenser is set downward for distillation, and stirring is continued while the

[2] *Org. Syntheses* Coll. Vol. **I**, 130 (1941).
[3] *Org. Syntheses*, **21**, 40 (1941).
[4] *Org. Syntheses* Coll. Vol. **I**, 38 (1941).

allyl cyanide is distilled into a 100-ml. distilling flask. Near the end of the distillation it may be necessary to discontinue stirring, and it is advisable to reduce the pressure somewhat to aid in the removal of the last portion of the product. The distillate is redistilled, and 50–53 g. (79–84%) of allyl cyanide boiling at 116–122° is collected. (Private communication from CURTIS W. SMITH and H. R. SNYDER; checked by W. E. BACHMANN and G. DANA JOHNSON.)

2. This amounts to 90–95 g. A separatory funnel of about 600-ml. capacity is the most convenient size.

3. The first ether extract contains 10 g. of nitrile; the second extract contains 4.5 g.

4. This procedure is shorter and less tedious than the more common method of drying and fractionating the ethereal solution.

5. A Dry Ice trap, inserted between the oil pump and the apparatus, condenses 5–10 g. of unchanged allyl cyanide. The yield of crude acid, after allowing for the recovered nitrile, is 62–72%.

6. This extraction removes about 1 g. of non-acidic impurity.

7. Ether can be substituted for chloroform without materially decreasing the yield.

8. This is prepared by diluting 16.5 ml. of concentrated sulfuric acid to 300 ml.

9. Contact with alkali results in the isomerization of vinylacetic acid to crotonic acid.

10. The first two extractions remove 27–28 g.; the last one, 3–4 g.

11. When cooled in a Dry Ice-acetone bath the acid should remain clear until it crystallizes at −36° to −35°. This indicates freedom from crotonic acid.[5]

[5] Fichter, *Ber.*, **35**, 938 (1902).

### 3. Methods of Preparation

The only practical methods for the preparation of vinylacetic acid involve hydrolysis of allyl cyanide; [6] carbonation of allylmagnesium bromide; [7, 8] or the malonic acid synthesis.[9]

[6] Falaise and Frognier, *Bull. soc. chim. Belg.*, **42**, 433 (1933) [*C.A.*, **28**, 2329 (1934)].

[7] Houben, *Ber.*, **36**, 2897 (1903).

[8] Gilman and McGlumphy, *Bull. soc. chim.*, (4) **43**, 1327 (1928).

[9] Linstead, Noble, and Boorman, *J. Chem. Soc.*, **1933**, 560.

## PRECAUTIONS IN USE OF POTASSIUM METAL

The use of potassium metal in carrying out organic reactions, or in preparing potassium alkoxides as reagents, is called for in a number of preparations. See *Coll. Vol.* **2**, p. 195; Vol. 23, pp. 42, 45.

Since potassium will burn in air, it is important to cut, slice, or powder the metal under an inert hydrocarbon solvent such as kerosene, toluene, or xylene. The air in the reaction flask should be displaced by an inert gas such as nitrogen. In this manner, fire hazard in handling potassium metal will be minimized.

# SUBJECT INDEX

*(This cumulative index comprises material from Volumes 20 through 24 of this series; for previous volumes see Collective Volumes I and 2.)*

Names in small capital letters refer to the titles of individual preparations. A number in ordinary bold-face type denotes the volume. A number in bold-face italics refers to a page which gives preparative directions for substances formed either as principal products or as by-products; numbers in ordinary type indicate pages on which a compound or a subject is mentioned in connection with other preparations. For example, Acetone cyanohydrin, **20,** 42, ***43,*** indicates that acetone cyanohydrin is mentioned on page 42, and that directions for its preparation are given in detail on page 43, of Volume 20.

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